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APPLICATION TRANSMITTAL LETTER

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Patricia K. Himmelfarb
(Typed or Printed Name of Person Mailing Paper or Fee)

Patricia K. Himmelfarb
(Signature of Person Mailing Paper or Fee)

Transmitted herewith for filing is the patent application of Doris COIT, Angelica MEDINA-SELBY, Mark SELBY and Michael HOUGHTON for NOVEL HCV NON-STRUCTURAL POLYPEPTIDE, claiming priority to provisional application serial no. 60/167,502, filed November 24, 1999.

Enclosed are:

- 100 sheets of drawings.
- ☐ A claim for foreign priority under 35 U.S.C. § 119/363 in ☐ a separate document ☐ the declaration.
- ☒ A claim for priority under 35 U.S.C. § 119(e)(1) in ☐ a separate document ☒ the declaration.
- ☐ A certified copy of the priority document.
- ☐ Verified Statement(s) Claiming Small Entity Status.
- ☒ Other: Sequence Listing (pp. 1-183); diskette; Statement to Support Filing and Submission in Accordance with 37 C.F.R. §§ 1.821-1.825; Title page; return receipt postcard.

The declaration of the inventor ☒ is enclosed ☒ unsigned.

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The fee has been calculated as follows:

A. Basic Application Fee		\$710
B. Total Claims $42 - 20 = 22$	x \$18	396
C. Independent Claims $2 - 3 = 0$	x \$80	0
D. If multiple dependent claims present, add	\$270	0
E. Total Application Fee (Total of A, B, C, & D)	=	<u>1106</u>
F. If small entity status is claimed, reduce Total Application Fee by 50%		0
G. Application Fee Due (E - F)	=	<u>1106</u>
H. Assignment Recording Fee of \$40.00 if assignment document is enclosed	\$40	<u>NA</u>
I. TOTAL FEE (G + H)		\$1106

Respectfully submitted,

Date: Nov 22, 2000

By: Dahna S. Pasternak
Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicants

CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-2708
Facsimile: (510) 655-3542

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Doricia K. Homenes
Typed or Printed Name of Person Mailing Paper or Fee

Doricia K. Homenes
Signature of Person Mailing Paper or Fee

Application for U.S. Letters Patent Entitled

NOVEL HCV NON-STRUCTURAL POLYPEPTIDE

claiming priority to provisional application serial no. 60/167,502, filed November 24, 1999

by Inventors:

Doris COIT
Angelica MEDINA-SELBY
Mark SELBY
Michael HOUGHTON

CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-2708
Facsimile: (510) 655-3542

Attorney Docket No. PP01617.002

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5 **NOVEL HCV NON-STRUCTURAL POLYPEPTIDE****CROSS-REFERENCE TO RELATED APPLICATION**

 This application is related to provisional patent application serial no. 60/167,502,
filed November 24, 1999 from which priority is claimed under 35 USC §119(e)(1) and
10 which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

 The present invention relates to polypeptides comprising a mutant non-structural
Hepatitis C virus ("HCV") polypeptide useful for immunogenic compounds for use against
15 HCV, methods of preparing and using the same, and immunogenic compositions
comprising the same. The present invention also relates to compositions comprising (a) a
mutant non-structural HCV polypeptide and (b) a viral polypeptide that is not a non-
structural HCV polypeptide and methods of using these compositions.

20 **BACKGROUND OF THE INVENTION**

 HCV is now recognized as the major agent of chronic hepatitis and liver disease
worldwide. It is estimated that HCV infects about 400 million people worldwide,
corresponding to more than 3% of the world population.

 Hepatitis C virus ("HCV") is a small enveloped RNA *flavivirus*, which contains a
25 positive-stranded RNA genome of about 10 kilobases. The genome has a single
uninterrupted ORF that encodes a protein of 3010-3011 amino acids. The structural
proteins of HCV include a core protein (C), which is highly immunogenic, as well as two
envelope proteins (E1 and E2), which likely form a heterodimer *in vivo*, and non-structural
proteins NS2-NS5. It is known that the NS3 region of the virus is important for post-
30 translational processing of the polyprotein into individual proteins, and the NS5 region
encodes an RNA-dependant RNA polymerase.

5 Virus-specific T lymphocytes, along with neutralizing antibodies, are the mainstay of the antiviral immune defense in established viral infections. Whereas CD8⁺ cytotoxic T cells eliminate virus-infected-cells, CD4⁺ T helper cells are essential for the efficient regulation of the antiviral immune response. CD4⁺ T helper cells recognize specific antigens as peptides bound to autologous HLA class II molecules (viral antigens or particles are taken up by professional antigen-presenting cells, processed to peptides, bound to HLA class II molecules in the lysosomal compartment, and transported back to the cell surface). Several observations support an important role of CD4⁺ T cells in the elimination of HCV infection. Tsai *et al.*, 1997 Hepatology 25:449-458; Diepolder et al 10 1995 Lancet 346: 1—6-1009; Missale et al 1996 JCI 98: 706-714; Botarelli et al 1993; Gastro 104: 580-587; Diepolder et al 1997 J.Virol 71: 6011. Immunogenic peptides usually have a minimal length of 8-11 amino acids. However, since the peptide binding groove of HLA class II molecules seems to be open at both ends, longer peptides are tolerated. Thus peptides eluted from HLA class II molecules are typically in the range of 15 15-25 amino acids. HLA class II molecules are extremely polymorphic and each allele seems to have its individual requirements for peptide binding. Thus the HLA class II repertoire of a given individual determines which viral peptides can be presented to T cells. Recognition of the specific HLA-peptide complex by the T cell receptor accompanied by appropriate costimulatory signals lead to T cell activation, secretion of cytokines, and T 20 cell proliferation.

Numerous studies demonstrate that HLA Class II restricted CD4⁺ responses are determined by stimulating peripheral blood mononuclear cells with recombinant viral antigens or peptides. Botarelli *et al.*, (1993) Gastroenterology 104:580-587; Farrari *et al.*, (1994) Hepatology 19:286-295; Minutello *et al.*, (1993) C. J. Exp. Med. 178:17-25; 25 Hoffmann *et al.*, (1995) Hepatology 21:632-638; Iwata *et al.*, (1995) Hepatology 22:1057-1064; and Tsai *et al.*, (1995) Hepatology 21:908-912.

Polyclonal multispecific CD8⁺ T cell responses have been detected in patients with chronic hepatitis C. Additionally, CD8⁺ CTL's were shown to be important in resolving acute HCV infection in chimpanzees (Cooper *et al.*, Immunity 1999). About 50% of 30 patients with chronic hepatitis C demonstrate a detectable virus-specific CD4⁺ T cell

response, which is most frequently directed against HCV core and/or NS4 and tends to be more common in patients who achieve sustained viral clearance during interferon- α therapy.

Depending on the pattern of lymphokines, CD4⁺ T helper cells have been classified as TH1, TH0, or TH2. Cytokines of the TH1 type are typically IFN- γ , lymphotoxin, and interleukin-2 (IL-2), which are believed to support activation of virus-specific CD8⁺ T cells and natural killer cells. The TH2 cytokines IL-4, IL-5, IL-10, and IL-13 are important for B cell activation and differentiation, thus inducing a humoral immune response.

During acute hepatitis C infection a strong and sustained TH1/TH0 response to NS3 and possibly to other nonstructural proteins is associated with a self-limited course of the disease. Diapolder *et al.*, (1995) Lancet 346:1006-1007, showed all CD4⁺ T cell clones to have a TH1 or TH0 cytokine profile, suggesting that the clones support cytotoxic immune mechanisms *in vivo*. The majority of CD4⁺ T cell clones responded to a relatively short segment of NS3, namely amino acids 1207-1278, suggesting that this region of NS3 is immunodominant for CD4⁺ T cells. More than 70% of those who contract HCV develop chronic infection and hepatitis, and a significant portion of them progress to cirrhosis and eventually hepatocellular carcinoma. The only approved therapy at present is a 6- to 12- month course of interferon α , which leads to sustained improvement in only 20% of patients. So far, no commercial vaccine is available.

Thus, there remains a need for compositions and methods capable of promoting anti-HCV responses.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to isolated polypeptides comprising mutant hepatitis C ("HCV") polypeptides comprising at least portions of NS3, NS4, and NS5. In a preferred aspect, NS3 is encoded by a nucleic acid sequence having an N-terminal deletion to remove the catalytic domain. The NS mutant polypeptides can include NS3, NS4s, NS4b, NS5a, NS5b or portions thereof. For example, in various embodiments, the mutant NS polypeptide comprises NS3, NS4 (NS4a and NS4b) and NS5 (NS5a and NS5b). In other embodiments, the NS polypeptide consists of NS3 and NS4 (for example,

NS4a and/or NS4b) or NS3 and NS5 (for example, NS5a and/or NS5b). Other combinations of full-length or fragments of non-structural components are also contemplated.

5 In another preferred aspect, the polypeptides further comprise a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other
10 genomes, such as, for example, polypeptides of HBV. Thus, the invention includes an isolated mutant non-structural ("NS") HCV polypeptide comprising a polypeptide having a mutation in the catalytic domain of NS3 that functionally disrupts the catalytic domain. The mutation can be, for example, a deletion or a substitution mutation. In certain embodiments, the mutant NS polypeptide comprises NS3, NS4 and NS5. In other
15 embodiments, the mutant NS polypeptides described herein further comprise a second viral polypeptide that is not NS3, NS4, or NS5 of HCV, for example an HCV Core polypeptide ("C"), or fragment thereof, or an HCV envelope protein ("E"), for example E1 and/or E2. In certain embodiments, C is truncated (*e.g.*, at amino acid 121).

20 In another aspect, the present invention relates to compositions comprising any of the mutant hepatitis C ("HCV") polypeptides described herein, for example polypeptides comprising at least portions of NS3, NS4, and NS5. In a preferred aspect, NS3 is encoded by a nucleic acid sequence having an N-terminal deletion to disrupt the function of the catalytic domain, for example by removing this domain. In another preferred aspect, the polypeptides further comprise a viral polypeptide that is not a non-structural HCV
25 polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for
30 example, polypeptides of HBV. In another aspect, the invention includes a composition

comprising (a) any of the polypeptides described herein; and (b) a pharmaceutically acceptable excipient (*e.g.*, carrier and/or adjuvant).

In another aspect, the invention includes an isolated and purified polynucleotide which encodes any of the mutant HCV polypeptides described herein. In certain
5 embodiments, the invention includes a composition comprising (a) the isolated purified polynucleotide encoding any of the mutant HCV polypeptides; and (b) a pharmaceutically acceptable excipient. The polynucleotide, can be for example, DNA in a plasmid, or is in a plasmid. Additionally, the polynucleotides described herein may be included in an expression vector as shown in the attached Figures and Sequence Listings.

10 In another aspect, the present invention relates to host cells transformed with expression vectors comprising a nucleic acid sequence encoding a mutant HCV polypeptide comprising at least portions of NS3, NS4, and NS5. In a preferred aspect, the expression vectors of the host cells further comprises at least one nucleic acid sequence encoding a viral polypeptide that is not a non-structural HCV polypeptide. Such
15 polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In
20 another preferred aspect the nucleic acid sequences of the expression vectors are coexpressed. In yet another preferred aspect, the host cells are yeast cells or mammalian cells.

In another aspect, the present invention relates to expression vectors comprising a nucleic acid sequence encoding a mutant HCV polypeptide comprising NS3, NS4, and
25 NS5. In a preferred aspect, the expression vectors of the host cells further comprises at least one nucleic acid sequence encoding a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Importantly, such polypeptides
30 need not be encoded by a natural HCV genome, such as, for example, truncated or

otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In another aspect, the present invention relates to methods of preparing a mutant HCV polypeptides. In a preferred aspect, the method comprises the steps of transforming a host cell with an expression vector, said vector comprising a nucleic acid sequence encoding a mutant HCV polypeptide comprising at least portions of NS3, NS4, and NS5, and isolating said polypeptide. In another preferred aspect the HCV polypeptide further comprises a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In another preferred aspect the host cells are yeast cells or mammalian cells.

In another aspect, the present invention relates to antibodies which specifically bind to mutant HCV polypeptide comprising NS3, NS4, and NS5, and to methods of making and using the same. In a preferred aspect, the HCV polypeptide further comprises a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, such as, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, and include, for example, polypeptides of HBV. In another preferred aspect, the antibody is either monoclonal or polyclonal.

In yet another aspect, a method of preparing a mutant NS HCV polypeptide, wherein the method comprises the steps of (a) transforming a host cell with any of the expression vectors described herein, under conditions wherein the polypeptide is expressed; and (b) isolating the polypeptide. The host cell can be, for example, a yeast cell, a mammalian cell a plant cell or an insect cell. The polypeptide can be expressed and isolated intracellularly or can be secreted and isolated from the surrounding environment.

In a still further aspect, a method of eliciting an immune response in a subject is provided. The immune response can be elicited by administering any of the polynucleotides and/or polypeptides described herein in one or multiple doses.

These and other embodiments of the subject invention will readily occur to those of skill in the art in light of the disclosure herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the cloning scheme for generating pCMV-NS35.

FIG. 2 shows the 9621bp vector pCMV-NS35.

FIG. 3 shows the nucleic acid sequence of pCMV-NS35 (SEQ ID NO:1), including the nucleic acid sequence of the NS35 ORF, and also the translation of NS35 (SEQ ID NO:2).

FIG. 4 shows the 9621bp pCMV-delNS35.

FIG. 5 shows the nucleic acid sequence of pCMV-delNS35 (SEQ ID NO:3), including the nucleic acid sequence of the delNS35 ORF, and also the translation of the delNS35 polypeptide (SEQ ID NO:4).

FIG. 6 shows the 4276bp pCMV-II.

FIG. 7 shows the nucleic acid sequence of pCMV-II (SEQ ID NO:5).

FIG. 8 shows the 6300bp pCMV-NS34A.

FIG. 9 shows the nucleic acid sequence of pCMV-NS34A (SEQ ID NO:6), including the nucleic acid sequence of the NS34A ORF, and also the translation of NS34A (SEQ ID NO:7).

FIG. 10 shows the cloning scheme for generating pd.ΔNS3NS5.

FIG. 11 shows the nucleic and amino acid sequences of pd.ΔNS3NS5 (SEQ ID NO:8 and 9).

FIG. 12 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.

FIG. 13 shows the cloning scheme for generating pd.ΔNS3NS5.pj.

FIG. 14 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj (SEQ ID NO:10 and 11).

FIG. 15 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.pj, specifically demonstrating the expression of ΔNS3NS5 polypeptide.

FIG. 16 shows the cloning scheme for generating pdΔNS3NS5.pj.core121RT and

5 pdΔNS3NS5.pj.core173RT.

FIG. 17 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj.core121 (SEQ ID NO:12 and 13).

FIG. 18 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj.core173 (SEQ ID NO:14 and 15).

10 FIG. 19 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.pj, specifically demonstrating the expression of ΔNS3NS5.core121 and ΔNS3NS5.core173 polypeptides. Lanes 1 and 7 show See Blue Standards. Lane 2 shows control yeast plasmid. Lanes 3 and 4 show ΔNS3NS5.core121RT polypeptide, colonies 1 and 2. Lanes 5 and 6 show
15 ΔNS3NS5.core173RT polypeptide, colonies 3 and 4.

FIG. 20 shows the cloning scheme for generating pdΔNS3NS5.pj.core140RT and pdΔNS3NS5.pj.core150RT.

FIG. 21 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj.core140 (SEQ ID NO:16 and 17).

20 FIG. 22 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj.core150 (SEQ ID NO:18 and 19).

FIG. 23 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.pj, specifically demonstrating the expression of ΔNS3NS5core140 and ΔNS3NS5core150 polypeptides. Lane 1 shows See Blue

25 Standards. Lanes 2 and 3 show ΔNS3NS5core140RT polypeptide, colonies 5 and 6. Lanes 4 and 5 show ΔNS3NS5core150RT polypeptide, colonies 7 and 8. Lane 6 shows control yeast plasmid. Lane 7 shows ΔNS3NS5core121RT polypeptide, colony 1. Lane 8 shows ΔNS3NS5core173RT polypeptide, colony 5.

DETAILED DESCRIPTION OF THE INVENTION

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology, microbiology, recombinant DNA techniques, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See e.g., Sambrook, et al., MOLECULAR CLONING; A LABORATORY MANUAL (1989); DNA CLONING, VOLUMES I AND II (D. N. Glover ed. 1985); OLIGONUCLEOTIDE SYNTHESIS (M. J. Gait ed., 1984); NUCLEIC ACID HYBRIDIZATION (B. D. Hames & S. J. Higgins eds. 1984); TRANSCRIPTION AND TRANSLATION (B. D. Hames & S. J. Higgins eds. 1984); ANIMAL CELL CULTURE (R. I. Freshney ed. 1986); IMMOBILIZED CELLS AND ENZYMES (IRL Press, 1986); B. Perbal, A PRACTICAL GUIDE TO MOLECULAR CLONING (1984); the series, METHODS OF ENZYMOLOGY (Academic Press, Inc.); GENE TRANSFER VECTORS FOR MAMMALIAN CELLS (J. H. Miller and M. P. Calos eds. 1987, Cold Springs Harbor Laboratory), Methods in Enzymology Vol. 154 and Vol. 155 (Wu and Grossman, and Wu, eds., respectively); Mayer and Walker eds. (1987), IMMUNOHISTOCHEMICAL METHODS IN CELL AND MOLECULAR BIOLOGY (Academic Press, London); Scopes, (1987), PROTEIN PURIFICATION: PRINCIPALS AND PRACTICE, Second Edition (Springer-Verlag, New York); and HANDBOOK OF EXPERIMENTAL IMMUNOLOGY, VOLUMES I-IV (D. M. Weir and C. C. Blackwell eds. 1986).

All publications, patents and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated by reference in their entirety.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "an antigen" includes a mixture of two or more antigens, and the like.

I. Definitions

In describing the present invention, the following terms will be employed, and are intended to be defined as indicated below.

The term "hepatitis C virus" (HCV) refers to an agent causative of Non-A, Non-B Hepatitis (NANBH). The nucleic acid sequence and putative amino acid sequence of HCV is described in U.S. Patent Nos. 5,856,437 and 5,350,671. The disease caused by HCV is called hepatitis C, formerly called NANBH. The term HCV, as used herein, denotes a viral species of which pathenogenic strains cause NANBH, as well as attenuated strains or defective interfering particles derived therefrom.

HCV is a member of the viral family flaviviridae. The morphology and composition of Flavivirus particles are known, and are discussed in Reed et al., *Curr. Stud. Hematol. Blood Transfus.* (1998), 62:1-37; HEPATITIS C VIRUSES IN FIELDS VIROLOGY (B.N. Fields, D.M. Knipe, P.M. Howley, eds.) (3d ed. 1996). It has recently been found that portions of the HCV genome are also homologous to pestiviruses.

Generally, with respect to morphology, Flaviviruses contain a central nucleocapsid surrounded by a lipid bilayer. Virions are spherical and have a diameter of about 40-50 nm. Their cores are about 25-30 nm in diameter. Along the outer surface of the virion envelope are projections that are about 5-10 nm long with terminal knobs about 2 nm in diameter.

The HCV genome is comprised of RNA. It is known that RNA containing viruses have relatively high rates of spontaneous mutation. Therefore, there can be multiple strains, which can be virulent or avirulent, within the HCV class or species. The ORF of HCV, including the translation spans of the core, non-structural, and envelope proteins, is shown in U.S. Patent Nos. 5,856,437 and 5,350,671.

The terms "polypeptide" and "protein" refer to a polymer of amino acid residues and are not limited to a minimum length of the product. Thus, peptides, oligopeptides, dimers, multimers, and the like, are included within the definition. Both full-length proteins and fragments thereof are encompassed by the definition. The terms also include postexpression modifications of the polypeptide, for example, glycosylation, acetylation, phosphorylation and the like. Furthermore, for purposes of the present invention, a

“polypeptide” refers to a protein which includes modifications, such as deletions, additions and substitutions (generally conservative in nature), to the native sequence, so long as the protein maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts which produce the proteins or errors due to PCR amplification.

An HCV polypeptide is a polypeptide, as defined above, derived from the HCV polyprotein. The polypeptide need not be physically derived from HCV, but may be synthetically or recombinantly produced. Moreover, the polypeptide may be derived from any of the various HCV strains, such as from strains 1, 2, 3 or 4 of HCV. A number of conserved and variable regions are known between these strains and, in general, the amino acid sequences of epitopes derived from these regions will have a high degree of sequence homology, e.g., amino acid sequence homology of more than 30%, preferably more than 40%, when the two sequences are aligned and homology determined by any of the programs or algorithms described herein. Thus, for example, the term “NS4” polypeptide refers to native NS4 from any of the various HCV strains, as well as NS4 analogs, muteins and immunogenic fragments, as defined further below.

Further, the terms “ΔNS35,” “delNS35,” “ΔNS3NS5,” and “ΔNS3-5” as used herein refer to a mutant polypeptide, comprising at least portions of NS3, NS4, or NS5, comprising a deletion in, or mutation of, the NS3 protease active site region to render the protease non-functional. In one embodiment, ΔNS3-5 comprises amino acids 1242-3011, as shown in FIG. 5, or polypeptides substantially homologous thereto. It will be readily apparent to one of ordinary skill in the art how to determine that NS3 protease has been rendered non-functional. If the protease is functional, one will obtain protein of the expected molecular weight upon expression. As set forth in Example 2 and Figure 15, using SDS-page, 4-20%, a protein having a molecular weight of approximately 194kD was obtained when strain AD3 was transformed with pd.ΔNS3NS5.PJ clone #5. One skilled in the art could readily determine whether a protein of the desired molecular weight was expressed for any given deletion or mutation.

The terms “analog” and “mutein” refer to biologically active derivatives of the reference molecule, or fragments of such derivatives, that retain desired activity, such as

the ability to stimulate a cell-mediated immune response, as defined below. In general, the term "analog" refers to compounds having a native polypeptide sequence and structure with one or more amino acid additions, substitutions (generally conservative in nature) and/or deletions, relative to the native molecule, so long as the modifications do not
5 destroy immunogenic activity. The term "mutein" refers to peptides having one or more peptide mimics ("peptoids"), such as those described in International Publication No. WO 91/04282. Preferably, the analog or mutein has at least the same immunoactivity as the native molecule. Methods for making polypeptide analogs and muteins are known in the art and are described further below.

10 Particularly preferred analogs include substitutions that are conservative in nature, i.e., those substitutions that take place within a family of amino acids that are related in their side chains. Specifically, amino acids are generally divided into four families: (1) acidic -- aspartate and glutamate; (2) basic -- lysine, arginine, histidine; (3) non-polar -- alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4)
15 uncharged polar -- glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. Phenylalanine, tryptophan, and tyrosine are sometimes classified as aromatic amino acids. For example, it is reasonably predictable that an isolated replacement of leucine with isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar conservative replacement of an amino acid with a structurally related amino acid, will not
20 have a major effect on the biological activity. For example, the polypeptide of interest may include up to about 5-10 conservative or non-conservative amino acid substitutions, or even up to about 15-25 conservative or non-conservative amino acid substitutions, or any integer between 5-25, so long as the desired function of the molecule remains intact. One of skill in the art may readily determine regions of the molecule of interest that can tolerate
25 change by reference to Hopp/Woods and Kyte-Doolittle plots, well known in the art.

By "fragment" is intended a polypeptide consisting of only a part of the intact full-length polypeptide sequence and structure. The fragment can include a C-terminal deletion and/or an N-terminal deletion of the native polypeptide. An "immunogenic fragment" of a particular HCV protein will generally include at least about 5-10 contiguous amino acid
30 residues of the full-length molecule, preferably at least about 15-25 contiguous amino acid

residues of the full-length molecule, and most preferably at least about 20-50 or more contiguous amino acid residues of the full-length molecule, that define an epitope, or any integer between 5 amino acids and the full-length sequence, provided that the fragment in question retains immunogenic activity, as measured by the assays described herein. For a description of various HCV epitopes, see, e.g., Chien et al., *Proc. Natl. Acad. Sci. USA* (1992) 89:10011-10015; Chien et al., *J. Gastroent. Hepatol.* (1993) 8:S33-39; Chien et al., International Publication No. WO 93/00365; Chien, D.Y., International Publication No. WO 94/01778; commonly owned, allowed U.S. Patent Application Serial Nos. 08/403,590 and 08/444,818.

The term "epitope" as used herein refers to a sequence of at least about 3 to 5, preferably about 5 to 10 or 15, and not more than about 1,000 amino acids (or any integer therebetween), which define a sequence that by itself or as part of a larger sequence, binds to an antibody generated in response to such sequence. There is no critical upper limit to the length of the fragment, which may comprise nearly the full-length of the protein sequence, or even a fusion protein comprising two or more epitopes from the HCV polyprotein. An epitope for use in the subject invention is not limited to a polypeptide having the exact sequence of the portion of the parent protein from which it is derived. Indeed, viral genomes are in a state of constant flux and contain several variable domains which exhibit relatively high degrees of variability between isolates. Thus the term "epitope" encompasses sequences identical to the native sequence, as well as modifications to the native sequence, such as deletions, additions and substitutions (generally conservative in nature).

Regions of a given polypeptide that include an epitope can be identified using any number of epitope mapping techniques, well known in the art. See, e.g., *Epitope Mapping Protocols* in *Methods in Molecular Biology*, Vol. 66 (Glenn E. Morris, Ed., 1996) Humana Press, Totowa, New Jersey. For example, linear epitopes may be determined by e.g., concurrently synthesizing large numbers of peptides on solid supports, the peptides corresponding to portions of the protein molecule, and reacting the peptides with antibodies while the peptides are still attached to the supports. Such techniques are known in the art and described in, e.g., U.S. Patent No. 4,708,871; Geysen et al. (1984) *Proc.*

Natl. Acad. Sci. USA 81:3998-4002; Geysen et al. (1986) *Molec. Immunol.* 23:709-715, all incorporated herein by reference in their entireties. Similarly, conformational epitopes are readily identified by determining spatial conformation of amino acids such as by, e.g., x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, e.g., *Epitope Mapping Protocols, supra*. Antigenic regions of proteins can also be identified using standard antigenicity and hydropathy plots, such as those calculated using, e.g., the Omega version 1.0 software program available from the Oxford Molecular Group. This computer program employs the Hopp/Woods method, Hopp et al., *Proc. Natl. Acad. Sci USA* (1981) 78:3824-3828 for determining antigenicity profiles, and the Kyte-Doolittle technique, Kyte et al., *J. Mol. Biol.* (1982) 157:105-132 for hydropathy plots.

As used herein, the term "conformational epitope" refers to a portion of a full-length protein, or an analog or mutein thereof, having structural features native to the amino acid sequence encoding the epitope within the full-length natural protein. Native structural features include, but are not limited to, glycosylation and three dimensional structure. Preferably, a conformational epitope is produced recombinantly and is expressed in a cell from which it is extractable under conditions which preserve its desired structural features, e.g. without denaturation of the epitope. Such cells include bacteria, yeast, insect, and mammalian cells. Expression and isolation of recombinant conformational epitopes from the HCV polyprotein are described in e.g., International Publication Nos. WO 96/04301, WO 94/01778, WO 95/33053, WO 92/08734, which applications are herein incorporated by reference in their entirety.

An "immunological response" to an HCV antigen (including both polypeptide and polynucleotides encoding polypeptides that are expressed *in vivo*) or composition is the development in a subject of a humoral and/or a cellular immune response to molecules present in the composition of interest. For purposes of the present invention, a "humoral immune response" refers to an immune response mediated by antibody molecules, while a "cellular immune response" is one mediated by T-lymphocytes and/or other white blood cells. One important aspect of cellular immunity involves an antigen-specific response by cytolytic T-cells ("CTLs"). CTLs have specificity for peptide antigens that are presented in association with proteins encoded by the major histocompatibility complex (MHC) and

expressed on the surfaces of cells. CTLs help induce and promote the intracellular destruction of intracellular microbes, or the lysis of cells infected with such microbes. Another aspect of cellular immunity involves an antigen-specific response by helper T-cells. Helper T-cells act to help stimulate the function, and focus the activity of,

5 nonspecific effector cells against cells displaying peptide antigens in association with MHC molecules on their surface. A “cellular immune response” also refers to the production of cytokines, chemokines and other such molecules produced by activated T-cells and/or other white blood cells, including those derived from CD4+ and CD8+ T-cells.

A composition or vaccine that elicits a cellular immune response may serve to

10 sensitize a vertebrate subject by the presentation of antigen in association with MHC molecules at the cell surface. The cell-mediated immune response is directed at, or near, cells presenting antigen at their surface. In addition, antigen-specific T-lymphocytes can be generated to allow for the future protection of an immunized host.

The ability of a particular antigen to stimulate a cell-mediated immunological

15 response may be determined by a number of assays, such as by lymphoproliferation (lymphocyte activation) assays, CTL cytotoxic cell assays, or by assaying for T-lymphocytes specific for the antigen in a sensitized subject. Such assays are well known in the art. See, e.g., Erickson et al., *J. Immunol.* (1993) 151:4189-4199; Doe et al., *Eur. J. Immunol.* (1994) 24:2369-2376; and the examples below.

20 Thus, an immunological response as used herein may be one which stimulates the production of CTLs, and/or the production or activation of helper T- cells. The antigen of interest may also elicit an antibody-mediated immune response. Hence, an immunological response may include one or more of the following effects: the production of antibodies by B-cells; and/or the activation of suppressor T-cells and/or $\gamma\delta$ T-cells directed specifically

25 to an antigen or antigens present in the composition or vaccine of interest. These responses may serve to neutralize infectivity, and/or mediate antibody-complement, or antibody dependent cell cytotoxicity (ADCC) to provide protection or alleviation of symptoms to an immunized host. Such responses can be determined using standard immunoassays and neutralization assays, well known in the art.

A "coding sequence" or a sequence which "encodes" a selected polypeptide, is a nucleic acid molecule which is transcribed (in the case of DNA) and translated (in the case of mRNA) into a polypeptide *in vitro* or *in vivo* when placed under the control of appropriate regulatory sequences. The boundaries of the coding sequence are determined by a start codon at the 5' (amino) terminus and a translation stop codon at the 3' (carboxy) terminus. A transcription termination sequence may be located 3' to the coding sequence.

A "nucleic acid" molecule or "polynucleotide" can include both double- and single-stranded sequences and refers to, but is not limited to, cDNA from viral, procaryotic or eucaryotic mRNA, genomic DNA sequences from viral (e.g. DNA viruses and retroviruses) or procaryotic DNA, and especially synthetic DNA sequences. The term also captures sequences that include any of the known base analogs of DNA and RNA.

"Operably linked" refers to an arrangement of elements wherein the components so described are configured so as to perform their desired function. Thus, a given promoter operably linked to a coding sequence is capable of effecting the expression of the coding sequence when the proper transcription factors, etc., are present. The promoter need not be contiguous with the coding sequence, so long as it functions to direct the expression thereof. Thus, for example, intervening untranslated yet transcribed sequences can be present between the promoter sequence and the coding sequence, as can transcribed introns, and the promoter sequence can still be considered "operably linked" to the coding sequence.

"Recombinant" as used herein to describe a nucleic acid molecule means a polynucleotide of genomic, cDNA, viral, semisynthetic, or synthetic origin which, by virtue of its origin or manipulation is not associated with all or a portion of the polynucleotide with which it is associated in nature. The term "recombinant" as used with respect to a protein or polypeptide means a polypeptide produced by expression of a recombinant polynucleotide. In general, the gene of interest is cloned and then expressed in transformed organisms, as described further below. The host organism expresses the foreign gene to produce the protein under expression conditions.

A "control element" refers to a polynucleotide sequence which aids in the expression of a coding sequence to which it is linked. The term includes promoters,

transcription termination sequences, upstream regulatory domains, polyadenylation signals, untranslated regions, including 5'-UTRs and 3'-UTRs and when appropriate, leader sequences and enhancers, which collectively provide for the transcription and translation of a coding sequence in a host cell.

5 A “promoter” as used herein is a DNA regulatory region capable of binding RNA polymerase in a host cell and initiating transcription of a downstream (3' direction) coding sequence operably linked thereto. For purposes of the present invention, a promoter sequence includes the minimum number of bases or elements necessary to initiate transcription of a gene of interest at levels detectable above background. Within the
10 promoter sequence is a transcription initiation site, as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. Eucaryotic promoters will often, but not always, contain “TATA” boxes and “CAT” boxes.

 A control sequence “directs the transcription” of a coding sequence in a cell when RNA polymerase will bind the promoter sequence and transcribe the coding sequence into
15 mRNA, which is then translated into the polypeptide encoded by the coding sequence.

 “Expression cassette” or “expression construct” refers to an assembly which is capable of directing the expression of the sequence(s) or gene(s) of interest. The expression cassette includes control elements, as described above, such as a promoter which is operably linked to (so as to direct transcription of) the sequence(s) or gene(s) of
20 interest, and often includes a polyadenylation sequence as well. Within certain embodiments of the invention, the expression cassette described herein may be contained within a plasmid construct. In addition to the components of the expression cassette, the plasmid construct may also include, one or more selectable markers, a signal which allows the plasmid construct to exist as single-stranded DNA (e.g., a M13 origin of replication), at
25 least one multiple cloning site, and a “mammalian” origin of replication (e.g., a SV40 or adenovirus origin of replication).

 “Transformation,” as used herein, refers to the insertion of an exogenous polynucleotide into a host cell, irrespective of the method used for insertion: for example, transformation by direct uptake, transfection, infection, and the like. For particular
30 methods of transfection, see further below. The exogenous polynucleotide may be

maintained as a nonintegrated vector, for example, an episome, or alternatively, may be integrated into the host genome.

A "host cell" is a cell which has been transformed, or is capable of transformation, by an exogenous DNA sequence.

5 By "isolated" is meant, when referring to a polypeptide, that the indicated molecule is separate and discrete from the whole organism with which the molecule is found in nature or is present in the substantial absence of other biological macromolecules of the same type. The term "isolated" with respect to a polynucleotide is a nucleic acid molecule devoid, in whole or part, of sequences normally associated with it in nature; or a sequence,
10 as it exists in nature, but having heterologous sequences in association therewith; or a molecule disassociated from the chromosome.

The term "purified" as used herein preferably means at least 75% by weight, more preferably at least 85% by weight, more preferably still at least 95% by weight, and most preferably at least 98% by weight, of biological macromolecules of the same type are
15 present.

"Homology" refers to the percent identity between two polynucleotide or two polypeptide moieties. Two DNA, or two polypeptide sequences are "substantially homologous" to each other when the sequences exhibit at least about 50% , preferably at least about 75%, more preferably at least about 80%-85%, preferably at least about 90%,
20 and most preferably at least about 95%-98%, or more, sequence identity over a defined length of the molecules. As used herein, substantially homologous also refers to sequences showing complete identity to the specified DNA or polypeptide sequence. The term "substantially homologous" as used herein in reference to Δ NS35 generally refers to an HCV nucleic or amino acid sequence that is at least 60% identical to the entire sequence of
25 the polypeptide encoded by Δ NS35 (see FIG. 5), where the sequence identity is preferably at least 75%, more preferably at least 80%, still more preferably at least about 85%, especially more than about 90%, most preferably 95% or greater, particularly 98% or greater. These homologous polypeptides include fragments, including mutants and allelic variants of the fragments. Identity between the two sequences is preferably determined by
30 the Smith-Waterman homology search algorithm as implemented in the MPSRCH program

(Oxford Molecular), using an affine gap search with parameters *gap open penalty*=12 and *gap extension penalty*=1. Thus, for example, the present invention includes an isolate which is 80% identical to a polypeptide encoded by ΔNS35. In some aspects of the invention, the polypeptide of the present invention is substantially homologous to the ΔNS35.

In general, "identity" refers to an exact nucleotide-to-nucleotide or amino acid-to-amino acid correspondence of two polynucleotides or polypeptide sequences, respectively. Percent identity can be determined by a direct comparison of the sequence information between two molecules by aligning the sequences, counting the exact number of matches between the two aligned sequences, dividing by the length of the shorter sequence, and multiplying the result by 100. Readily available computer programs can be used to aid in the analysis, such as ALIGN, Dayhoff, M.O. in *Atlas of Protein Sequence and Structure* M.O. Dayhoff ed., 5 Suppl. 3:353-358, National biomedical Research Foundation, Washington, DC, which adapts the local homology algorithm of Smith and Waterman *Advances in Appl. Math.* 2:482-489, 1981 for peptide analysis. Programs for determining nucleotide sequence identity are available in the Wisconsin Sequence Analysis Package, Version 8 (available from Genetics Computer Group, Madison, WI) for example, the BESTFIT, FASTA and GAP programs, which also rely on the Smith and Waterman algorithm. These programs are readily utilized with the default parameters recommended by the manufacturer and described in the Wisconsin Sequence Analysis Package referred to above. For example, percent identity of a particular nucleotide sequence to a reference sequence can be determined using the homology algorithm of Smith and Waterman with a default scoring table and a gap penalty of six nucleotide positions.

Another method of establishing percent identity in the context of the present invention is to use the MPSRCH package of programs copyrighted by the University of Edinburgh, developed by John F. Collins and Shane S. Sturrok, and distributed by IntelliGenetics, Inc. (Mountain View, CA). From this suite of packages the Smith-Waterman algorithm can be employed where default parameters are used for the scoring table (for example, gap open penalty of 12, gap extension penalty of one, and a gap of six). From the data generated the "Match" value reflects "sequence identity." Other suitable

programs for calculating the percent identity or similarity between sequences are generally known in the art, for example, another alignment program is BLAST, used with default parameters. For example, BLASTN and BLASTP can be used using the following default parameters: genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10; 5 Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + Swiss protein + Spupdate + PIR. Details of these programs can be found at the following internet address: <http://www.ncbi.nlm.gov/cgi-bin/BLAST>.

Alternatively, homology can be determined by hybridization of polynucleotides 10 under conditions which form stable duplexes between homologous regions, followed by digestion with single-stranded-specific nuclease(s), and size determination of the digested fragments. DNA sequences that are substantially homologous can be identified in a Southern hybridization experiment under, for example, stringent conditions, as defined for that particular system. Defining appropriate hybridization conditions is within the skill of 15 the art. See, e.g., Sambrook et al., *supra*; *DNA Cloning, supra*; *Nucleic Acid Hybridization, supra*.

“Stringency” refers to conditions in a hybridization reaction that favor association of very similar sequences over sequences that differ. For example, the combination of temperature and salt concentration should be chosen that is approximately 120 to 200°C 20 below the calculated T_m of the hybrid under study. The temperature and salt conditions can often be determined empirically in preliminary experiments in which samples of genomic DNA immobilized on filters are hybridized to the sequence of interest and then washed under conditions of different stringencies. See Sambrook *et al.* at page 9.50.

Variables to consider when performing, for example, a Southern blot are (1) the 25 complexity of the DNA being blotted and (2) the homology between the probe and the sequences being detected. The total amount of the fragment(s) to be studied can vary a magnitude of 10, from 0.1 to 1 μ g for a plasmid or phage digest to 10^{-9} to 10^{-8} g for a single copy gene in a highly complex eukaryotic genome. For lower complexity polynucleotides, substantially shorter blotting, hybridization, and exposure times, a smaller amount of 30 starting polynucleotides, and lower specific activity of probes can be used. For example, a

single-copy yeast gene can be detected with an exposure time of only 1 hour starting with 1 µg of yeast DNA, blotting for two hours, and hybridizing for 4-8 hours with a probe of 10⁸ cpm/µg. For a single-copy mammalian gene a conservative approach would start with 10 µg of DNA, blot overnight, and hybridize overnight in the presence of 10% dextran sulfate using a probe of greater than 10⁸ cpm/µg, resulting in an exposure time of ~24 hours.

Several factors can affect the melting temperature (T_m) of a DNA-DNA hybrid between the probe and the fragment of interest, and consequently, the appropriate conditions for hybridization and washing. In many cases the probe is not 100% homologous to the fragment. Other commonly encountered variables include the length and total G+C content of the hybridizing sequences and the ionic strength and formamide content of the hybridization buffer. The effects of all of these factors can be approximated by a single equation:

$$T_m = 81 + 16.6(\log_{10} C_i) + 0.4[\%(G + C)] - 0.6(\%\text{formamide}) - 600/n - 1.5(\%\text{mismatch}).$$
where C_i is the salt concentration (monovalent ions) and *n* is the length of the hybrid in base pairs (slightly modified from Meinkoth & Wahl (1984) *Anal. Biochem.* 138: 267-284). In general, convenient hybridization temperatures in the presence of 50% formamide are 42°C for a probe with is 95% to 100% homologous to the target fragment, 37°C for 90% to 95% homology, and 32°C for 85% to 90% homology. For lower homologies, formamide content should be lowered and temperature adjusted accordingly, using the equation above. If the homology between the probe and the target fragment are not known, the simplest approach is to start with both hybridization and wash conditions which are nonstringent. If non-specific bands or high background are observed after autoradiography, the filter can be washed at high stringency and reexposed. If the time required for exposure makes this approach impractical, several hybridization and/or washing stringencies should be tested in parallel.

By "nucleic acid immunization" is meant the introduction of a nucleic acid molecule encoding one or more selected antigens into a host cell, for the *in vivo* expression of the antigen or antigens. The nucleic acid molecule can be introduced directly into the recipient subject, such as by injection, inhalation, oral, intranasal and mucosal administration, or the like, or can be introduced *ex vivo*, into cells which have been

removed from the host. In the latter case, the transformed cells are reintroduced into the subject where an immune response can be mounted against the antigen encoded by the nucleic acid molecule.

An "open reading frame" or ORF is a region of a polynucleotide sequence which encodes a polypeptide; this region can represent a portion of a coding sequence or a total coding sequence.

As used herein, the term "antibody" refers to a polypeptide or group of polypeptides which comprise at least one antigen binding site. An "antigen binding site" is formed from the folding of the variable domains of an antibody molecule(s) to form three-dimensional binding sites with an internal surface shape and charge distribution complementary to the features of an epitope of an antigen, which allows specific binding to form an antibody-antigen complex. An antigen binding site may be formed from a heavy- and/or light-chain domain (VH and VL, respectively), which form hypervariable loops which contribute to antigen binding. The term "antibody" includes, without limitation, polyclonal antibodies, monoclonal antibodies, chimeric antibodies, altered antibodies, univalent antibodies, Fab proteins, and single-domain antibodies. In many cases, the binding phenomena of antibodies to antigens is equivalent to other ligand/anti-ligand binding.

If polyclonal antibodies are desired, a selected mammal (e.g., mouse, rabbit, goat, horse, etc.) is immunized with an immunogenic polypeptide bearing an HCV epitope(s). Serum from the immunized animal is collected and treated according to known procedures. If serum containing polyclonal antibodies to an HCV epitope contains antibodies to other antigens, the polyclonal antibodies can be purified by immunoaffinity chromatography. Techniques for producing and processing polyclonal antisera are known in the art, see for example, Mayer and Walker, eds. (1987) IMMUNOCHEMICAL METHODS IN CELL AND MOLECULAR BIOLOGY (Academic Press, London).

Monoclonal antibodies directed against HCV epitopes can also be readily produced by one skilled in the art. The general methodology for making monoclonal antibodies by hybridomas is well known. Immortal antibody-producing cell lines can be created by cell fusion, and also by other techniques such as direct transformation of B lymphocytes with oncogenic DNA, or transfection with Epstein-Barr virus. See, e.g., M. Schreier et al.

(1980) HYBRIDOMA TECHNIQUES; Hammerling et al. (1981), MONOCLONAL ANTIBODIES AND T-CELL HYBRIDOMAS; Kennett et al. (1980) MONOCLONAL ANTIBODIES; see also, U.S. Pat. Nos. 4,341,761; 4,399,121; 4,427,783; 4,444,887; 4,466,917; 4,472,500; 4,491,632; and 4,493,890. Panels of monoclonal antibodies
5 produced against HCV epitopes can be screened for various properties; i.e., for isotype, epitope affinity, etc. As used herein, a "single domain antibody" (dAb) is an antibody which is comprised of an HL domain, which binds specifically with a designated antigen. A dAb does not contain a VL domain, but may contain other antigen binding domains known to exist to antibodies, for example, the kappa and lambda domains. Methods for
10 preparing dabs are known in the art. See, for example, Ward et al, Nature 341: 544 (1989).

Antibodies can also be comprised of VH and VL domains, as well as other known antigen binding domains. Examples of these types of antibodies and methods for their preparation and known in the art (see, e.g., U.S. Pat. No. 4,816,467, which is incorporated herein by reference), and include the following. For example, "vertebrate antibodies" refers
15 to antibodies which are tetramers or aggregates thereof, comprising light and heavy chains which are usually aggregated in a "Y" configuration and which may or may not have covalent linkages between the chains. In vertebrate antibodies, the amino acid sequences of the chains are homologous with those sequences found in antibodies produced in vertebrates, whether in situ or in vitro (for example, in hybridomas). Vertebrate antibodies
20 include, for example, purified polyclonal antibodies and monoclonal antibodies, methods for the preparation of which are described infra.

"Hybrid antibodies" are antibodies where chains are separately homologous with reference to mammalian antibody chains and represent novel assemblies of them, so that two different antigens are precipitable by the tetramer or aggregate. In hybrid antibodies,
25 one pair of heavy and light chains are homologous to those found in an antibody raised against a first antigen, while a second pair of chains are homologous to those found in an antibody raised against a second antibody. This results in the property of "divalence", i.e., the ability to bind two antigens simultaneously. Such hybrids can also be formed using chimeric chains, as set forth below.

"Chimeric antibodies" refers to antibodies in which the heavy and/or light chains are fusion proteins. Typically, one portion of the amino acid sequences of the chain is homologous to corresponding sequences in an antibody derived from a particular species or a particular class, while the remaining segment of the chain is homologous to the sequences derived from another species and/or class. Usually, the variable region of both light and heavy chains mimics the variable regions or antibodies derived from one species of vertebrates, while the constant portions are homologous to the sequences in the antibodies derived from another species of vertebrates. However, the definition is not limited to this particular example. Also included is any antibody in which either or both of the heavy or light chains are composed of combinations of sequences mimicking the sequences in antibodies of different sources, whether these sources be from differing classes or different species of origin, and whether or not the fusion point is at the variable/constant boundary. Thus, it is possible to produce antibodies in which neither the constant nor the variable region mimic known antibody sequences. It then becomes possible, for example, to construct antibodies whose variable region has a higher specific affinity for a particular antigen, or whose constant region can elicit enhanced complement fixation, or to make other improvements in properties possessed by a particular constant region.

Another example is "altered antibodies", which refers to antibodies in which the naturally occurring amino acid sequence in a vertebrate antibody has been varied. Utilizing recombinant DNA techniques, antibodies can be redesigned to obtain desired characteristics. The possible variations are many, and range from the changing of one or more amino acids to the complete redesign of a region, for example, the constant region. Changes in the constant region, in general, to attain desired cellular process characteristics, e.g., changes in complement fixation, interaction with membranes, and other effector functions. Changes in the variable region can be made to alter antigen binding characteristics. The antibody can also be engineered to aid the specific delivery of a molecule or substance to a specific cell or tissue site. The desired alterations can be made by known techniques in molecular biology, e.g., recombinant techniques, site-directed mutagenesis, etc.

Yet another example are "univalent antibodies", which are aggregates comprised of a heavy-chain/light-chain dimer bound to the Fc (i.e., stem) region of a second heavy chain. This type of antibody escapes antigenic modulation. See, e.g., Glennie et al. Nature 295: 712 (1982). Included also within the definition of antibodies are "Fab" fragments of antibodies. The "Fab" region refers to those portions of the heavy and light chains which are roughly equivalent, or analogous, to the sequences which comprise the branch portion of the heavy and light chains, and which have been shown to exhibit immunological binding to a specified antigen, but which lack the effector Fc portion. "Fab" includes aggregates of one heavy and one light chain (commonly known as Fab'), as well as tetramers containing the 2H and 2L chains (referred to as F(ab)2), which are capable of selectively reacting with a designated antigen or antigen family. Fab antibodies can be divided into subsets analogous to those described above, i.e., "vertebrate Fab", "hybrid Fab", "chimeric Fab", and "altered Fab". Methods of producing Fab fragments of antibodies are known within the art and include, for example, proteolysis, and synthesis by recombinant techniques.

"Antigen-antibody complex" refers to the complex formed by an antibody that is specifically bound to an epitope on an antigen.

"Immunogenic polypeptide" refers to a polypeptide that elicits a cellular and/or humoral immune response in a mammal, whether alone or linked to a carrier, in the presence or absence of an adjuvant.

"Antigenic determinant" refers to the site on an antigen or hapten to which a specific antibody molecule or specific cell surface receptor binds.

As used herein, "treatment" refers to any of (i) the prevention of infection or reinfection, as in a traditional vaccine, (ii) the reduction or elimination of symptoms, and (iii) the substantial or complete elimination of the pathogen in question. Treatment may be effected prophylactically (prior to infection) or therapeutically (following infection).

By "vertebrate subject" is meant any member of the subphylum cordata, including, without limitation, humans and other primates, including non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including

rodents such as mice, rats and guinea pigs; birds, including domestic, wild and game birds such as chickens, turkeys and other gallinaceous birds, ducks, geese, and the like. The term does not denote a particular age. Thus, both adult and newborn individuals are intended to be covered. The invention described herein is intended for use in any of the
5 above vertebrate species, since the immune systems of all of these vertebrates operate similarly.

II. Modes of Carrying out the Invention

Before describing the present invention in detail, it is to be understood that this
10 invention is not limited to particular formulations or process parameters as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

Although a number of compositions and methods similar or equivalent to those
15 described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

General Overview

An aim of an HCV vaccine is to generate broad immunity to a wide breadth of
20 antigens because HCV is so divergent and because humoral as well as cellular immune responses are desirable to combat this human pathogen. While antibodies generated against the envelope glycoprotein(s) might aid in virus neutralization, there is additional benefit to be derived from a vaccine that includes other regions. The likelihood of T-helper responses generated against a polypeptide would be helpful in a vaccine setting as would
25 generation of cytotoxic T cells. The non-structural region represents such a candidate antigen, but processing by the protease generates several polypeptides, making purification complicated. It would be advantageous, therefore, to derive a non-structural cassette that is unprocessed by the NS3 protease.

The present invention solves this and other problems using compositions and
30 methods involving an N-terminal deletion in NS3, which removes the catalytic domain.

As such, some or all of the remainder of the non-structural region (through NS5B) is expressed as an intact polypeptide. Expression of this species has been documented in mammalian cells as well as in yeast. Further, in certain aspects, polynucleotides encoding HCV core polypeptides (or fragments thereof) are added (*e.g.*, operably linked) to the carboxy-terminus of the non-structural cassette. As the core coding region is relatively highly conserved among HCV isolates, the presence of this region may enhance the immune response. Because core has at its C-terminus a very hydrophobic domain (amino acids 174-191), shorter versions of core were also engineered onto the polypeptide. As described in detail herein, the truncation of core to amino acid 121 yielded higher expression than the amino acid 173 truncation when engineered onto the C-terminus of the mutant NS polypeptide. The combination of most of the non-structural region fused to a C-terminally truncated core into a polypeptide is novel and has advantages for vaccine immunization. Moreover, because the aim is not necessarily to generate antibody responses to this polypeptide, there is no need to maintain a native conformation, enabling a more facile purification protocol.

Mutant HCV Non-Structural Polypeptides

Genomes of HCV strains contain a single open reading frame of approximately 9,000 to 12,000 nucleotides, which is transcribed into a polyprotein. An HCV polyprotein is cleaved to produce at least ten distinct products, in the order of NH₂- Core-E1-E2-p7-NS2-NS3-NS4a-NS4b-NS5a-NS5b-COOH. Mutant HCV polypeptides of the invention contain an N-terminal deletion in NS3, which removes or disables the catalytic domain. Preferably, the polypeptides also include the remainder of the non-structural region, although in certain embodiments, the polypeptides may include less than all of the remaining NS polypeptides, for example mutant NS polypeptides including any combinations of NS2-NS3-NS4a-NS4b-NS5a-NS5b (*e.g.*, NS3NS3-NS5a-NS5b; NS3-NS4a-NS4b; NS3-NS4a-NS4b-NS5a; NS3-NS4b-NS5a-NS5b; NS3-NS4a-NS5a; NS3-NS4b-NS5a; NS3-NS4b-NS5b; etc.).

The HCV NS3 protein functions as a protease and a helicase and occurs at approximately amino acid 1027 to amino acid 1657 of the polyprotein (numbered relative

to HCV-1). See Choo *et al.* (1991) Proc. Natl. Acad. Sci. USA 88:2451-2455. HCV NS4 occurs at approximately amino acid 1658 to amino acid 1972, NS5a occurs at approximately amino acid 1973 to amino acid 2420, and HCV NS5b occurs at approximately amino acid 2421 to amino acid 3011 of the polyprotein (numbered relative to HCV-1) (Choo *et al.*, 1991).

The mutant polypeptides described herein can either be full-length polypeptides or portions of NS3, NS4 (NS4a and NS4b), NS5a, and NS5b polypeptides. Epitopes of NS3, NS4 (NS4a and NS4b), NS5a, NS5b, NS3NS4NS5a, and NS3NS4NS5aNS5b can be identified by several methods. For example, NS3, NS4, NS5a, NS5b polypeptides or fusion proteins comprising any combination of the above, can be isolated, for example, by immunoaffinity purification using a monoclonal antibody for the polypeptide or protein. The isolated protein sequence can then be screened by preparing a series of short peptides by proteolytic cleavage of the purified protein, which together span the entire protein sequence. By starting with, for example, 100-mer polypeptides, each polypeptide can be tested for the presence of epitopes recognized by a T cell receptor on an HCV-activated T cell, progressively smaller and overlapping fragments can then be tested from an identified 100-mer to map the epitope of interest.

Epitopes recognized by a T cell receptor on an HCV-activated T cell can be identified by, for example, ⁵¹Cr release assay (see Example 2) or by lymphoproliferation assay (see Example 4). In a ⁵¹Cr release assay, target cells can be constructed that display the epitope of interest by cloning a polynucleotide encoding the epitope into an expression vector and transforming the expression vector into the target cells. Non-structural polypeptides can occur in any order in the fusion protein. If desired, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more of one or more of the polypeptides may occur in the fusion protein. Multiple viral strains of HCV occur, and NS3, NS4, NS5a, and NS5b polypeptides of any of these strains can be used in a fusion protein.

Nucleic acid and amino acid sequences of a number of HCV strains and isolates, including nucleic acid and amino acid sequences of NS3, NS4, NS5a, NS5b genes and polypeptides have been determined. For example, isolate HCV J1.1 is described in Kubo *et al.* (1989) Japan. Nucl. Acids Res. 17:10367-10372; Takeuchi *et al.* (1990) Gene

91:287-291; Takeuchi *et al.* (1990) J. Gen. Virol. 71:3027-3033; and Takeuchi *et al.* (1990) Nucl. Acids Res. 18:4626. The complete coding sequences of two independent isolates, HCV-J and BK, are described by Kato *et al.*, (1990) Proc. Natl. Acad. Sci. USA 87:9524-9528 and Takamizawa *et al.*, (1991) J. Virol. 65:1105-1113 respectively.

5 Publications that describe HCV-1 isolates include Choo *et al.* (1990) Brit. Med. Bull. 46:423-441; Choo *et al.* (1991) Proc. Natl. Acad. Sci. USA 88:2451-2455 and Han *et al.* (1991) Proc. Natl. Acad. Sci. USA 88:1711-1715. HCV isolates HC-J1 and HC-J4 are described in Okamoto *et al.* (1991) Japan J. Exp. Med. 60:167-177. HCV isolates HCT 18~, HCT 23, Th, HCT 27, EC1 and EC10 are described in Weiner *et al.* (1991) Virol. 10 180:842-848. HCV isolates Pt-1, HCV-K1 and HCV-K2 are described in Enomoto *et al.* (1990) Biochem. Biophys. Res. Commun. 170:1021-1025. HCV isolates A, C, D & E are described in Tsukiyama-Kohara *et al.* (1991) Virus Genes 5:243-254.

Each of the mutant HCV polypeptides containing at least portions of NS3, NS4 and NS5 can be obtained from the same HCV strain or isolate or from different HCV strains or isolates. Thus, each non-structural region of the polypeptide can be from the same HCV 15 strain or isolate or from each different HCV strains or isolates. In addition to the mutant HCV non-structural polypeptides described herein, the proteins can contain other polypeptides derived from the HCV polyprotein. For example, it may be desirable to include polypeptides derived from the core region of the HCV polyprotein. This region 20 occurs at amino acid positions 1-191 of the HCV polyprotein, numbered relative to HCV-1. Either the full-length protein or epitopes of the full-length protein may be used in the subject fusions, such as those epitopes found between amino acids 10-53, amino acids 10-45, amino acids 67-88, amino acids 120-130, or any of the core epitopes identified in, e.g., Houghton *et al.*, U.S. Patent No. 5,350,671; Chien *et al.*, *Proc. Natl. Acad. Sci. USA* (1992) 25 89:10011-10015; Chien *et al.*, *J. Gastroent. Hepatol.* (1993) 8:S33-39; Chien *et al.*, International Publication No. WO 93/00365; Chien, D.Y., International Publication No. WO 94/01778; and commonly owned, U.S. Patent No. 6,150,087, the disclosures of which are incorporated herein by reference in their entirety. When present, additional non-structural HCV polypeptides such as core can be obtained from the same HCV strain or 30 isolate or from different HCV strains or isolates.

Preferably, the above-described mutant proteins, as well as the individual components of these proteins, are produced recombinantly. A polynucleotide encoding these proteins can be introduced into an expression vector which can be expressed in a suitable expression system. A variety of bacterial, yeast, mammalian, insect and plant expression systems are available in the art and any such expression system can be used. Optionally, a polynucleotide encoding these proteins can be translated in a cell-free translation system. Such methods are well known in the art. The proteins also can be constructed by solid phase protein synthesis.

If desired, the mutant polypeptides, or the individual components of these polypeptides, also can contain other amino acid sequences, such as amino acid linkers or signal sequences, as well as ligands useful in protein purification, such as glutathione-S-transferase and staphylococcal protein A.

Polynucleotides

The polynucleotides of the present invention are not necessarily physically derived from the nucleotide sequences shown, but can be generated in any manner, including, for example, chemical synthesis or DNA replication or reverse transcription or transcription. In addition, combinations of regions corresponding to that of the designated sequences can be modified in ways known to the art to be consistent with an intended use.

The DNA encoding the desired polypeptide, whether in fused or mature form, and whether or not containing a signal sequence to permit secretion, can be ligated into expression vectors suitable for any convenient host. Both eukaryotic and prokaryotic host systems are presently used in forming recombinant polypeptides, and a summary of some of the more common control systems and host cell is given below. The polypeptide produced in such host cells is then isolated from lysed cells or from the culture medium and purified to the extent needed for its intended use.

Purification can be by techniques known in the art, for example, differential extraction, salt fractionation, chromatography on ion exchange resins, affinity chromatography, centrifugation, alkali resolubilization of insoluble protein, and the like.

See, for example, Methods in Enzymology for a variety of methods for purifying proteins.

Polynucleotides contain less than an entire HCV genome and can be RNA or single- or double-stranded DNA. Preferably, the polynucleotides are isolated free of other components, such as proteins and lipids. Polynucleotides of the invention can also comprise other nucleotide sequences, such as sequences coding for linkers, signal
5 sequences, or ligands useful in protein purification such as glutathione-S-transferase and staphylococcal protein A.

Polynucleotides encoding mutant HCV non-structural polypeptides can be isolated from a genomic library derived from nucleic acid sequences present in, for example, the plasma, serum, or liver homogenate of an HCV infected individual or can be synthesized in
10 the laboratory, for example, using an automatic synthesizer. An amplification method such as PCR can be used to amplify polynucleotides from either HCV genomic DNA or cDNA.

Further, while the polypeptides that are not NS3, NS4, or NS5 of HCV of the present invention can comprise a substantially complete viral domain, in many applications all that is required is that the polypeptide comprise an antigenic or immunogenic region of
15 the virus. An antigenic region of a polypeptide is generally relatively small-typically 8 to 10 amino acids or less in length. Fragments of as few as 5 amino acids can characterize an antigenic region. These segments can correspond to regions of, for example, C, E1, or E2 epitopes. Accordingly, using the cDNAs of C, E1, or E2 as a basis, DNAs encoding short segments of C, E1, or E2 polypeptides can be expressed recombinantly either as fusion
20 proteins, or as isolated polypeptides. In addition, short amino acid sequences can be conveniently obtained by chemical synthesis.

Polynucleotides encoding the polypeptides described herein can comprise coding sequences for these polypeptides which occur naturally or can be artificial sequences which do not occur in nature. These polynucleotides can be ligated to form a coding sequence for
25 the fusion proteins using standard molecular biology techniques. If desired, polynucleotides can be cloned into an expression vector and transformed into, for example, bacterial, yeast, insect, plant or mammalian cells so that the fusion proteins of the invention can be expressed in and isolated from a cell culture.

The expression of polypeptides containing these domains in a variety of
30 recombinant host cells, including, for example, bacteria, yeast, insect, plant and vertebrate

cells, give rise to important immunological reagents which can be used for diagnosis, detection, and vaccines.

The general techniques used in extracting the genome from a virus, preparing and probing a cDNA library, sequencing clones, constructing expression vectors, transforming
5 cells, performing immunological assays such as radioimmunoassays and. ELISA assays, for growing cells in culture, and the like are known in the art and laboratory manuals are available describing these techniques. However, as a general guide, the following sets forth some sources currently available for such procedures, and for materials useful in carrying them out.

10 Both prokaryotic and eukaryotic host cells may be used for expression of desired coding sequences when appropriate control sequences which are compatible with the designated host are used. Among prokaryotic hosts, *E. coli* is most frequently used. Expression control sequences for prokaryotes include promoters, optionally containing operator portions, and ribosome binding sites. Transfer vectors compatible with
15 prokaryotic hosts are commonly derived from, for example, pBR322, a plasmid containing operons conferring ampicillin and tetracycline resistance, and the various pUC vectors, which also contain sequences conferring antibiotic resistance markers. These markers may be used to obtain successful transformants by selection. Commonly used prokaryotic control sequences include the Beta-lactamase (penicillinase) and lactose promoter systems
20 (Chang et al. (1977), *Nature* 198:1056), the tryptophan (*trp*) promoter system (Goeddel et al. (1980) *Nucleic Acid Res.* 8:4057), the lambda-derived P[L] promoter and N gene ribosome binding site (Shimatake et al. (1981) *Nature* 292:128) and the hybrid *tac* promoter (De Boer et al. (1983) *Proc. Natl. Acad. Sci. U.S.A.* 292:128) derived from sequences of the *trp* and *lac* UV5 promoters. The foregoing systems are particularly
25 compatible with *E. coli*; if desired, other prokaryotic hosts such as strains of *Bacillus* or *Pseudomonas* may be used, with corresponding control sequences.

Eukaryotic hosts include mammalian and yeast cells in culture systems. Mammalian cell lines available as hosts for expression are known in the art and include many immortalized cell lines available from the American Type Culture Collection
30 (ATCC), including HeLa cells, Chinese hamster ovary (CHO) cells, baby hamster kidney

(BHK) cells, and a number of other cell lines. Suitable promoters for mammalian cells are also known in the art and include viral promoters such as that from Simian Virus 40 (SV40) (Fiers (1978), Nature 273:113), Rous sarcoma virus (RSV), adenovirus (ADV), and bovine papilloma virus (BPV). Mammalian cells may also require terminator
5 sequences and poly A addition sequences; enhancer sequences which increase expression may also be included, and sequences which cause amplification of the gene may also be desirable. These sequences are known in the art. Vectors suitable for replication in mammalian cells may include viral replicons, or sequences which insure integration of the appropriate sequences encoding NANBV epitopes into the host genome.

10 The vaccinia virus system can also be used to express foreign DNA in mammalian cells. To express heterologous genes, the foreign DNA is usually inserted into the thymidine kinase gene of the vaccinia virus and then infected cells can be selected. This procedure is known in the art and further information can be found in these references (Mackett et al. J. Virol. 49: 857-864 (1984) and Chapter 7 in DNA Cloning, Vol. 2, IRL
15 Press).

Yeast expression systems are also known to one of ordinary skill in the art. A yeast promoter is any DNA sequence capable of binding yeast RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*e.g.*, structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to
20 the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site (the "TATA Box") and a transcription initiation site. A yeast promoter may also have a second domain called an upstream activator sequence (UAS), which, if present, is usually distal to the structural gene. The UAS permits regulated (inducible) expression. Constitutive expression occurs in the absence of a UAS.
25 Regulated expression may be either positive or negative, thereby either enhancing or reducing transcription.

Yeast is a fermenting organism with an active metabolic pathway, therefore sequences encoding enzymes in the metabolic pathway provide particularly useful promoter sequences. Examples include alcohol dehydrogenase (ADH) (EP-A-0 284 044),
30 enolase, glucokinase, glucose-6-phosphate isomerase, glyceraldehyde-3-phosphate-

dehydrogenase (GAP or GAPDH), hexokinase, phosphofructokinase, 3-phosphoglycerate mutase, and pyruvate kinase (PyK) (EPO-A-0 329 203). The yeast *PHO5* gene, encoding acid phosphatase, also provides useful promoter sequences (Myanohara *et al.* (1983) *Proc. Natl. Acad. Sci. USA* 80:1).

5 In addition, synthetic promoters which do not occur in nature also function as yeast promoters. For example, UAS sequences of one yeast promoter may be joined with the transcription activation region of another yeast promoter, creating a synthetic hybrid promoter. Examples of such hybrid promoters include the ADH regulatory sequence linked to the GAP transcription activation region (US Patent Nos. 4,876,197 and
10 4,880,734). Other examples of hybrid promoters include promoters which consist of the regulatory sequences of either the *ADH2*, *GAL4*, *GAL10*, OR *PHO5* genes, combined with the transcriptional activation region of a glycolytic enzyme gene such as GAP or PyK (EP-A-0 164 556). Furthermore, a yeast promoter can include naturally occurring promoters of non-yeast origin that have the ability to bind yeast RNA polymerase and initiate
15 transcription. Examples of such promoters include, *inter alia*, (Cohen *et al.* (1980) *Proc. Natl. Acad. Sci. USA* 77:1078; Henikoff *et al.* (1981) *Nature* 283:835; Hollenberg *et al.* (1981) *Curr. Topics Microbiol. Immunol.* 96:119; Hollenberg *et al.* (1979) "The Expression of Bacterial Antibiotic Resistance Genes in the Yeast *Saccharomyces cerevisiae*," in: *Plasmids of Medical, Environmental and Commercial Importance* (eds.
20 K.N. Timmis and A. Puhler); Mercerau-Puigalon *et al.* (1980) *Gene* 11:163; Panthier *et al.* (1980) *Curr. Genet.* 2:109).

A DNA molecule may be expressed intracellularly in yeast. A promoter sequence may be directly linked with the DNA molecule, in which case the first amino acid at the N-terminus of the recombinant protein will always be a methionine, which is encoded by the
25 ATG start codon. If desired, methionine at the N-terminus may be cleaved from the protein by *in vitro* incubation with cyanogen bromide.

Fusion proteins provide an alternative for yeast expression systems, as well as in mammalian, baculovirus, and bacterial expression systems. Usually, a DNA sequence encoding the N-terminal portion of an endogenous yeast protein, or other stable protein, is
30 fused to the 5' end of heterologous coding sequences. Upon expression, this construct will

provide a fusion of the two amino acid sequences. For example, the yeast or human superoxide dismutase (SOD) gene, can be linked at the 5' terminus of a foreign gene and expressed in yeast. The DNA sequence at the junction of the two amino acid sequences may or may not encode a cleavable site. See *e.g.*, EP-A-0 196 056. Another example is a ubiquitin fusion protein. Such a fusion protein is made with the ubiquitin region that preferably retains a site for a processing enzyme (*e.g.*, ubiquitin-specific processing protease) to cleave the ubiquitin from the foreign protein. Through this method, therefore, native foreign protein can be isolated (*e.g.*, WO88/024066).

Alternatively, foreign proteins can also be secreted from the cell into the growth media by creating chimeric DNA molecules that encode a fusion protein comprised of a leader sequence fragment that provide for secretion in yeast of the foreign protein. Preferably, there are processing sites encoded between the leader fragment and the foreign gene that can be cleaved either *in vivo* or *in vitro*. The leader sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids which direct the secretion of the protein from the cell.

DNA encoding suitable signal sequences can be derived from genes for secreted yeast proteins, such as the yeast invertase gene (EP-A-0 012 873; JPO. 62,096,086) and the A-factor gene (US patent 4,588,684). Alternatively, leaders of non-yeast origin, such as an interferon leader, exist that also provide for secretion in yeast (EP-A-0 060 057).

A preferred class of secretion leaders are those that employ a fragment of the yeast alpha-factor gene, which contains both a "pre" signal sequence, and a "pro" region. The types of alpha-factor fragments that can be employed include the full-length pre-pro alpha factor leader (about 83 amino acid residues) as well as truncated alpha-factor leaders (usually about 25 to about 50 amino acid residues) (US Patents 4,546,083 and 4,870,008; EP-A-0 324 274). Additional leaders employing an alpha-factor leader fragment that provides for secretion include hybrid alpha-factor leaders made with a presequence of a first yeast, but a pro-region from a second yeast alphafactor. (*e.g.*, see WO 89/02463.)

Usually, transcription termination sequences recognized by yeast are regulatory regions located 3' to the translation stop codon, and thus together with the promoter flank the coding sequence. These sequences direct the transcription of an mRNA which can be

translated into the polypeptide encoded by the DNA. Examples of transcription terminator sequence and other yeast-recognized termination sequences, such as those coding for glycolytic enzymes.

Usually, the above described components, comprising a promoter, leader (if desired), coding sequence of interest, and transcription termination sequence, are put together into expression constructs. Expression constructs are often maintained in a replicon, such as an extrachromosomal element (*e.g.*, plasmids) capable of stable maintenance in a host, such as yeast or bacteria. The replicon may have two replication systems, thus allowing it to be maintained, for example, in yeast for expression and in a prokaryotic host for cloning and amplification. Examples of such yeast-bacteria shuttle vectors include YEp24 (Botstein *et al.* (1979) *Gene* 8:17-24), pCl/1 (Brake *et al.* (1984) *Proc. Natl. Acad. Sci USA* 81:4642-4646), and YRp17 (Stinchcomb *et al.* (1982) *J. Mol. Biol.* 158:157). In addition, a replicon may be either a high or low copy number plasmid. A high copy number plasmid will generally have a copy number ranging from about 5 to about 200, and usually about 10 to about 150. A host containing a high copy number plasmid will preferably have at least about 10, and more preferably at least about 20. Enter a high or low copy number vector may be selected, depending upon the effect of the vector and the foreign protein on the host. See *e.g.*, Brake *et al.*, *supra*.

Alternatively, the expression constructs can be integrated into the yeast genome with an integrating vector. Integrating vectors usually contain at least one sequence homologous to a yeast chromosome that allows the vector to integrate, and preferably contain two homologous sequences flanking the expression construct. Integrations appear to result from recombinations between homologous DNA in the vector and the yeast chromosome (Orr-Weaver *et al.* (1983) *Methods in Enzymol.* 101:228-245). An integrating vector may be directed to a specific locus in yeast by selecting the appropriate homologous sequence for inclusion in the vector. See Orr-Weaver *et al.*, *supra*. One or more expression construct may integrate, possibly affecting levels of recombinant protein produced (Rine *et al.* (1983) *Proc. Natl. Acad. Sci. USA* 80:6750). The chromosomal sequences included in the vector can occur either as a single segment in the vector, which results in the integration of the entire vector, or two segments homologous to adjacent

segments in the chromosome and flanking the expression construct in the vector, which can result in the stable integration of only the expression construct.

Usually, extrachromosomal and integrating expression constructs may contain selectable markers to allow for the selection of yeast strains that have been transformed.

5 Selectable markers may include biosynthetic genes that can be expressed in the yeast host, such as *ADE2*, *HIS4*, *LEU2*, *TRP1*, and *ALG7*, and the G418 resistance gene, which confer resistance in yeast cells to tunicamycin and G418, respectively. In addition, a suitable selectable marker may also provide yeast with the ability to grow in the presence of toxic compounds, such as metal. For example, the presence of *CUP1* allows yeast to grow in the
10 presence of copper ions (Butt *et al.* (1987) *Microbiol. Rev.* 51:351).

Alternatively, some of the above described components can be put together into transformation vectors. Transformation vectors are usually comprised of a selectable marker that is either maintained in a replicon or developed into an integrating vector, as described above.

15 Expression and transformation vectors, either extrachromosomal replicons or integrating vectors, have been developed for transformation into many yeasts. For example, expression vectors have been developed for, *inter alia*, the following yeasts: *Candida albicans* (Kurtz, *et al.* (1986) *Mol. Cell. Biol.* 6:142), *Candida maltosa* (Kunze, *et al.* (1985) *J. Basic Microbiol.* 25:141). *Hansenula polymorpha* (Gleeson, *et al.* (1986) *J. Gen. Microbiol.* 132:3459; Roggenkamp *et al.* (1986) *Mol. Gen. Genet.* 202:302),
20 *Kluyveromyces fragilis* (Das, *et al.* (1984) *J. Bacteriol.* 158:1165), *Kluyveromyces lactis* (De Louvencourt *et al.* (1983) *J. Bacteriol.* 154:737; Van den Berg *et al.* (1990) *Bio/Technology* 8:135), *Pichia guillermondii* (Kunze *et al.* (1985) *J. Basic Microbiol.* 25:141), *Pichia pastoris* (Cregg, *et al.* (1985) *Mol. Cell. Biol.* 5:3376; US Patent Nos.
25 4,837,148 and 4,929,555), *Saccharomyces cerevisiae* (Hinnen *et al.* (1978) *Proc. Natl. Acad. Sci. USA* 75:1929; Ito *et al.* (1983) *J. Bacteriol.* 153:163), *Schizosaccharomyces pombe* (Beach and Nurse (1981) *Nature* 300:706), and *Yarrowia lipolytica* (Davidow, *et al.* (1985) *Curr. Genet.* 10:380471 Gaillardin, *et al.* (1985) *Curr. Genet.* 10:49).

Methods of introducing exogenous DNA into yeast hosts are well-known in the art,
30 and usually include either the transformation of spheroplasts or of intact yeast cells treated

with alkali cations. Transformation procedures usually vary with the yeast species to be transformed. (See *e.g.*, Kurtz *et al.* (1986) *Mol. Cell. Biol.* 6:142; Kunze *et al.* (1985) *J. Basic Microbiol.* 25:141; Candida; Gleeson *et al.* (1986) *J. Gen. Microbiol.* 132:3459; Roggenkamp *et al.* (1986) *Mol. Gen. Genet.* 202:302; Hansenula; Das *et al.* (1984) *J. Bacteriol.* 158:1165; De Louvencourt *et al.* (1983) *J. Bacteriol.* 154:1165; Van den Berg *et al.* (1990) *Bio/Technology* 8:135; Kluyveromyces; Cregg *et al.* (1985) *Mol. Cell. Biol.* 5:3376; Kunze *et al.* (1985) *J. Basic Microbiol.* 25:141; US Patent Nos. 4,837,148 and 4,929,555; Pichia; Hinnen *et al.* (1978) *Proc. Natl. Acad. Sci. USA* 75:1929; Ito *et al.* (1983) *J. Bacteriol.* 153:163 Saccharomyces; Beach and Nurse (1981) *Nature* 300:706; Schizosaccharomyces; Davidow *et al.* (1985) *Curr. Genet.* 10:39; Gaillardin *et al.* (1985) *Curr. Genet.* 10:49; Yarrowia).

Bacterial expression techniques are known in the art. A bacterial promoter is any DNA sequence capable of binding bacterial RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*e.g.*, structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site and a transcription initiation site. A bacterial promoter may also have a second domain called an operator, that may overlap an adjacent RNA polymerase binding site at which RNA synthesis begins. The operator permits negative regulated (inducible) transcription, as a gene repressor protein may bind the operator and thereby inhibit transcription of a specific gene. Constitutive expression may occur in the absence of negative regulatory elements, such as the operator. In addition, positive regulation may be achieved by a gene activator protein binding sequence, which, if present is usually proximal (5') to the RNA polymerase binding sequence. An example of a gene activator protein is the catabolite activator protein (CAP), which helps initiate transcription of the lac operon in Escherichia coli (E. coli) (Raibaud *et al.* (1984) *Annu. Rev. Genet.* 18:173). Regulated expression may therefore be either positive or negative, thereby either enhancing or reducing transcription.

Expression and transformation vectors, either extra-chromosomal replicons or integrating vectors, have been developed for transformation into many bacteria. For

example, expression vectors have been developed for, *inter alia*, the following bacteria:
 Bacillus subtilis (Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA* 79:5582; EP-A-0 036
 259 and EP-A-0 063 953; WO 84/04541), Escherichia coli (Shimatake *et al.* (1981)
Nature 292:128; Amann *et al.* (1985) *Gene* 40:183; Studier *et al.* (1986) *J. Mol. Biol.*
 5 189:113; EP-A-0 036 776, EP-A-0 136 829 and EP-A-0 136 907), Streptococcus cremoris
 (Powell *et al.* (1988) *Appl. Environ. Microbiol.* 54:655); Streptococcus lividans (Powell
et al. (1988) *Appl. Environ. Microbiol.* 54:655), Streptomyces lividans (US patent
 4,745,056).

Methods of introducing exogenous DNA into bacterial hosts are well-known in the
 10 art, and usually include either the transformation of bacteria treated with CaCl₂ or other
 agents, such as divalent cations and DMSO. DNA can also be introduced into bacterial
 cells by electroporation. Transformation procedures usually vary with the bacterial species
 to be transformed. (See *e.g.*, Masson *et al.* (1989) *FEMS Microbiol. Lett.* 60:273; Palva
et al. (1982) *Proc. Natl. Acad. Sci. USA* 79:5582; EP-A-0 036 259 and EP-A-0 063 953;
 15 WO 84/04541, Bacillus, Miller *et al.* (1988) *Proc. Natl. Acad. Sci.* 85:856; Wang *et al.*
 (1990) *J. Bacteriol.* 172:949; Campylobacter, Cohen *et al.* (1973) *Proc. Natl. Acad.*
Sci. 69:2110; Dower *et al.* (1988) *Nucleic Acids Res.* 16:6127; Kushner (1978) "An
 improved method for transformation of Escherichia coli with ColE1-derived plasmids. *In*
Genetic Engineering: Proceedings of the International Symposium on Genetic Engineering
 20 (eds. H.W. Boyer and S. Nicosia); Mandel *et al.* (1970) *J. Mol. Biol.* 53:159; Taketo
 (1988) *Biochim. Biophys. Acta* 949:318; Escherichia; Chassy *et al.* (1987) *FEMS*
Microbiol. Lett. 44:173 Lactobacillus; Fiedler *et al.* (1988) *Anal. Biochem* 170:38,
 Pseudomonas; Augustin *et al.* (1990) *FEMS Microbiol. Lett.* 66:203, Staphylococcus,
 Barany *et al.* (1980) *J. Bacteriol.* 144:698; Harlander (1987) "Transformation of
 25 Streptococcus lactis by electroporation, in: *Streptococcal Genetics* (ed. J. Ferretti and R.
 Curtiss III); Perry *et al.* (1981) *Infect. Immun.* 32:1295; Powell *et al.* (1988) *Appl.*
Environ. Microbiol. 54:655; Somkuti *et al.* (1987) *Proc. 4th Evr. Cong. Biotechnology*
I:412, Streptococcus).

In addition, viral antigens can be expressed in insect cells by the Baculovirus
 30 system. A general guide to Baculovirus expression by Summer and Smith is A Manual of

Methods for Baculovirus Vectors and Insect Cell Culture Procedures (Texas Agricultural Experiment Station Bulletin No. 1555). To incorporate the heterologous gene into the Baculovirus genome the gene is first cloned into a transfer vector containing some Baculovirus sequences. This transfer vector, when it is cotransfected with wild-type virus
5 into insect cells, will recombine with the wild-type virus. Usually, the transfer vector will be engineered so that the heterologous gene will disrupt the wild-type Baculovirus polyhedron gene. This disruption enables easy selection of the recombinant virus since the cells infected with the recombinant virus will appear phenotypically different from the cells infected with the wild-type virus. The purified recombinant virus can be used to infect cells
10 to express the heterologous gene. The foreign protein can be secreted into the medium if a signal peptide is linked in frame to the heterologous gene; otherwise, the protein will be bound in the cell lysates. For further information, see Smith et al Mol. & Cell. Biol. 3:2156-2165 (1983) or Luckow and Summers in Virology 17: 31-39 (1989).

Baculovirus expression can also be affected in plant cells. There are many plant
15 cell culture and whole plant genetic expression systems known in the art. Exemplary plant cellular genetic expression systems include those described in patents, such as: US 5,693,506; US 5,659,122; and US 5,608,143. Additional examples of genetic expression in plant cell culture has been described by Zenk, *Phytochemistry* 30:3861-3863 (1991). Descriptions of plant protein signal peptides may be found in addition to the references
20 described above in Vaulcombe et al., *Mol. Gen. Genet.* 209:33-40 (1987); Chandler et al., *Plant Molecular Biology* 3:407-418 (1984); Rogers, *J. Biol. Chem.* 260:3731-3738 (1985); Rothstein et al., *Gene* 55:353-356 (1987); Whittier et al., *Nucleic Acids Research* 15:2515-2535 (1987); Wirsal et al., *Molecular Microbiology* 3:3-14 (1989); Yu et al., *Gene* 122:247-253 (1992). A description of the regulation of plant gene expression by the
25 phytohormone, gibberellic acid and secreted enzymes induced by gibberellic acid can be found in R.L. Jones and J. MacMillin, Gibberellins: in: *Advanced Plant Physiology*, Malcolm B. Wilkins, ed., 1984 Pitman Publishing Limited, London, pp. 21-52. References that describe other metabolically-regulated genes: Sheen, *Plant Cell*, 2:1027-1038(1990); Maas et al., *EMBO J.* 9:3447-3452 (1990); Benkel and Hickey, *Proc. Natl.*
30 *Acad. Sci.* 84:1337-1339 (1987).

All plants from which protoplasts can be isolated and cultured to give whole regenerated plants can be transformed by the present invention so that whole plants are recovered which contain the transferred gene. It is known that practically all plants can be regenerated from cultured cells or tissues, including but not limited to all major species of
5 sugarcane, sugar beet, cotton, fruit and other trees, legumes and vegetables. Some suitable plants include, for example, species from the genera *Fragaria*, *Lotus*, *Medicago*, *Onobrychis*, *Trifolium*, *Trigonella*, *Vigna*, *Citrus*, *Linum*, *Geranium*, *Manihot*, *Daucus*, *Arabidopsis*, *Brassica*, *Raphanus*, *Sinapis*, *Atropa*, *Capsicum*, *Datura*, *Hyoscyamus*, *Lycopersion*, *Nicotiana*, *Solanum*, *Petunia*, *Digitalis*, *Majorana*, *Cichorium*, *Helianthus*,
10 *Lactuca*, *Bromus*, *Asparagus*, *Antirrhinum*, *Hererocallis*, *Nemesia*, *Pelargonium*, *Panicum*, *Pennisetum*, *Ranunculus*, *Senecio*, *Salpiglossis*, *Cucumis*, *Browaalia*, *Glycine*, *Lolium*, *Zea*, *Triticum*, *Sorghum*, and *Datura*.

Transformation can be by any method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus and transducing a host
15 cell with the virus, and by direct uptake of the polynucleotide. The transformation procedure used depends upon the host to be transformed. Bacterial transformation by direct uptake generally employs treatment with calcium or rubidium chloride (Cohen (1972), Proc. Natl. Acad. Sci. U.S.A. 69:2110; Maniatis et al. (1982), MOLECULAR CLONING; A LABORATORY MANUAL (Cold Spring Harbor Press, Cold Spring Harbor, N.Y.).
20 Yeast transformation by direct uptake may be carried out using the method of Hinnen et al. (1978) Proc. Natl. Acad. Sci. U.S.A. 75: 1929. Mammalian transformations by direct uptake may be conducted using the calcium phosphate precipitation method of Graham and Van der Eb (1978), Virology 52:546 or the various known modifications thereof.

Vector construction employs techniques which are known in the art. Site-specific
25 DNA cleavage is performed by treating with suitable restriction enzymes under conditions which generally are specified by the manufacturer of these commercially available enzymes. The cleaved fragments may be separated using polyacrylamide or agarose gel electrophoresis techniques, according to the general procedures found in Methods in Enzymology (1980) 65:499-560. Sticky ended cleavage fragments may be blunt ended
30 using E. coli DNA polymerase I (Klenow) in the presence of the appropriate

deoxynucleotide triphosphates (dNTPs) present in the mixture. Treatment with S1 nuclease may also be used, resulting in the hydrolysis of any single stranded DNA portions.

Ligations are carried out using standard buffer and temperature conditions using T4 DNA ligase and ATP; sticky end ligations require less ATP and less ligase than blunt end ligations. When vector fragments are used as part of a ligation mixture, the vector fragment is often treated with bacterial alkaline phosphatase (BAP) or calf intestinal alkaline phosphatase to remove the 5'-phosphate and thus prevent religation of the vector; alternatively, restriction enzyme digestion of unwanted fragments can be used to prevent ligation. Ligation mixtures are transformed into suitable cloning hosts, such as *E. coli*, and successful transformants selected by, for example, antibiotic resistance, and screened for the correct construction.

Synthetic oligonucleotides may be prepared using an automated oligonucleotide synthesizer as described by Warner (1984), DNA 3:401. If desired, the synthetic strands may be labeled with ^{32}P by treatment with polynucleotide kinase in the presence of ^{32}P -ATP, using standard conditions for the reaction. DNA sequences, including those isolated from cDNA libraries, may be modified by known techniques, including, for example site directed mutagenesis, as described by Zoller (1982), Nucleic Acids Res. 10:6487.

The expression constructs of the present invention, including the desired fusion, or individual expression constructs comprising the individual components of these fusions, may be used for nucleic acid immunization, to activate HCV-specific T cells, using standard gene delivery protocols. Methods for gene delivery are known in the art. See, e.g., U.S. Patent Nos. 5,399,346, 5,580,859, 5,589,466, incorporated by reference herein in their entireties. Genes can be delivered either directly to the vertebrate subject or, alternatively, delivered *ex vivo*, to cells derived from the subject and the cells reimplanted in the subject. For example, the constructs can be delivered as plasmid DNA, e.g., contained within a plasmid, such as pBR322, pUC, or ColE1

Additionally, the expression constructs can be packaged in liposomes prior to delivery to the cells. Lipid encapsulation is generally accomplished using liposomes which are able to stably bind or entrap and retain nucleic acid. The ratio of condensed DNA to lipid preparation can vary but will generally be around 1:1 (mg DNA:micromoles lipid), or

more of lipid. For a review of the use of liposomes as carriers for delivery of nucleic acids, see, Hug and Sleight, *Biochim. Biophys. Acta.* (1991) 1097:1-17; Straubinger et al., in *Methods of Enzymology* (1983), Vol. 101, pp. 512-527.

Liposomal preparations for use with the present invention include cationic
5 (positively charged), anionic (negatively charged) and neutral preparations, with cationic liposomes particularly preferred. Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy]propyl]-N,N,N-triethylammonium (DOTMA) liposomes are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, NY. (See, also, Felgner et al., *Proc. Natl. Acad. Sci. USA* (1987) 84:7413-7416). Other commercially available
10 lipids include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer). Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g., Szoka et al., *Proc. Natl. Acad. Sci. USA* (1978) 75:4194-4198; PCT Publication No. WO 90/11092 for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. The various liposome-nucleic
15 acid complexes are prepared using methods known in the art. See, e.g., Straubinger et al., in *METHODS OF IMMUNOLOGY* (1983), Vol. 101, pp. 512-527; Szoka et al., *Proc. Natl. Acad. Sci. USA* (1978) 75:4194-4198; Papahadjopoulos et al., *Biochim. Biophys. Acta* (1975) 394:483; Wilson et al., *Cell* (1979) 17:77; Deamer and Bangham, *Biochim. Biophys. Acta* (1976) 443:629; Ostro et al., *Biochem. Biophys. Res. Commun.* (1977)
20 76:836; Fraley et al., *Proc. Natl. Acad. Sci. USA* (1979) 76:3348; Enoch and Strittmatter, *Proc. Natl. Acad. Sci. USA* (1979) 76:145; Fraley et al., *J. Biol. Chem.* (1980) 255:10431; Szoka and Papahadjopoulos, *Proc. Natl. Acad. Sci. USA* (1978) 75:145; and Schaefer-Ridder et al., *Science* (1982) 215:166.

The DNA can also be delivered in cochleate lipid compositions similar to those
25 described by Papahadjopoulos et al., *Biochem. Biophys. Acta.* (1975) 394:483-491. See, also, U.S. Patent Nos. 4,663,161 and 4,871,488.

A number of viral based systems have been developed for gene transfer into mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems, such as murine sarcoma virus, mouse mammary tumor virus, Moloney
30 murine leukemia virus, and Rous sarcoma virus. A selected gene can be inserted into a

vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to cells of the subject either *in vivo* or *ex vivo*. A number of retroviral systems have been described (U.S. Patent No. 5,219,740; Miller and Rosman, *BioTechniques* (1989) 7:980-990; Miller, A.D., *Human Gene Therapy* (1990) 1:5-14; Scarpa et al., *Virology* (1991) 180:849-852; Burns et al., *Proc. Natl. Acad. Sci. USA* (1993) 90:8033-8037; and Boris-Lawrie and Temin, *Cur. Opin. Genet. Develop.* (1993) 3:102-109. Briefly, retroviral gene delivery vehicles of the present invention may be readily constructed from a wide variety of retroviruses, including for example, B, C, and D type retroviruses as well as spumaviruses and lentiviruses such as FIV, HIV, HIV-1, HIV-2 and SIV (see RNA Tumor Viruses, Second Edition, Cold Spring Harbor Laboratory, 1985). Such retroviruses may be readily obtained from depositories or collections such as the American Type Culture Collection ("ATCC"; 10801 University Blvd., Manassas, VA 20110-2209), or isolated from known sources using commonly available techniques.

A number of adenovirus vectors have also been described, such as adenovirus Type 2 and Type 5 vectors. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham, *J. Virol.* (1986) 57:267-274; Bett et al., *J. Virol.* (1993) 67:5911-5921; Mittereder et al., *Human Gene Therapy* (1994) 5:717-729; Seth et al., *J. Virol.* (1994) 68:933-940; Barr et al., *Gene Therapy* (1994) 1:51-58; Berkner, K.L. *BioTechniques* (1988) 6:616-629; and Rich et al., *Human Gene Therapy* (1993) 4:461-476).

Molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al., *J. Biol. Chem.* (1993) 268:6866-6869 and Wagner et al., *Proc. Natl. Acad. Sci. USA* (1992) 89:6099-6103, can also be used for gene delivery.

Members of the Alphavirus genus, such as but not limited to vectors derived from the Sindbis and Semliki Forest viruses, VEE, will also find use as viral vectors for delivering the gene of interest. For a description of Sindbis-virus derived vectors useful for the practice of the instant methods, see, Dubensky et al., *J. Virol.* (1996) 70:508-519; and International Publication Nos. WO 95/07995 and WO 96/17072.

Other vectors can be used, including but not limited to simian virus 40, cytomegalovirus. Bacterial vectors, such as *Salmonella* ssp. *Yersinia enterocolitica*, *Shigella* spp., *Vibrio cholerae*, *Mycobacterium* strain BCG, and *Listeria monocytogenes* can be used. Minichromosomes such as MC and MC1, bacteriophages, cosmids (plasmids into which phage lambda *cos* sites have been inserted) and replicons (genetic elements that are capable of replication under their own control in a cell) can also be used.

The expression constructs may also be encapsulated, adsorbed to, or associated with, particulate carriers. Such carriers present multiple copies of a selected molecule to the immune system and promote trapping and retention of molecules in local lymph nodes. The particles can be phagocytosed by macrophages and can enhance antigen presentation through cytokine release. Examples of particulate carriers include those derived from polymethyl methacrylate polymers, as well as microparticles derived from poly(lactides) and poly(lactide-co-glycolides), known as PLG. See, e.g., Jeffery et al., *Pharm. Res.* (1993) 10:362-368; and McGee et al., *J. Microencap.* (1996).

A wide variety of other methods can be used to deliver the expression constructs to cells. Such methods include DEAE dextran-mediated transfection, calcium phosphate precipitation, polylysine- or polyornithine-mediated transfection, or precipitation using other insoluble inorganic salts, such as strontium phosphate, aluminum silicates including bentonite and kaolin, chromic oxide, magnesium silicate, talc, and the like. Other useful methods of transfection include electroporation, sonoporation, protoplast fusion, liposomes, peptoid delivery, or microinjection. See, e.g., Sambrook et al., *supra*, for a discussion of techniques for transforming cells of interest; and Felgner, P.L., *Advanced Drug Delivery Reviews* (1990) 5:163-187, for a review of delivery systems useful for gene transfer. One particularly effective method of delivering DNA using electroporation is described in International Publication No. WO/0045823.

Additionally, biolistic delivery systems employing particulate carriers such as gold and tungsten, are especially useful for delivering the expression constructs of the present invention. The particles are coated with the construct to be delivered and accelerated to high velocity, generally under a reduced atmosphere, using a gun powder discharge from a "gene gun." For a description of such techniques, and apparatuses useful therefore, see,

e.g., U.S. Patent Nos. 4,945,050; 5,036,006; 5,100,792; 5,179,022; 5,371,015; and 5,478,744.

Compositions

5 The invention also provides compositions comprising the HCV polypeptides or polynucleotides described herein. Such compositions are useful as diagnostics, for example, using the mutant polypeptides (or polynucleotides encoding these polypeptides) in diagnostic reagents. Diagnostics using polypeptides and polynucleotides are known to those of skill in the art.

10 In addition, immunogenic compounds can be prepared from one or more immunogenic polypeptides derived from the polypeptides described herein, for example the ΔNS35 polypeptide. The preparation of immunogenic compounds which contain immunogenic polypeptide(s) as active ingredients is known to one skilled in the art. Typically, such immunogenic compounds are prepared as injectables, either as liquid
15 solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified, or the protein encapsulated in liposomes.

 Immunogenic and diagnostic compositions of the invention preferably comprise a pharmaceutically acceptable carrier. The carrier should not itself induce the production of
20 antibodies harmful to the host. Pharmaceutically acceptable carriers are well known to those in the art. Such carriers include, but are not limited to, large, slowly metabolized, macromolecules, such as proteins, polysaccharides such as latex functionalized sepharose, agarose, cellulose, cellulose beads and the like, polylactic acids, polyglycolic acids, polymeric amino acids such as polyglutamic acid, polylysine, and the like, amino acid
25 copolymers, and inactive virus particles.

 Pharmaceutically acceptable salts can also be used in compositions of the invention, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as salts of organic acids such as acetates, propionates, malonates, or benzoates. Especially useful protein substrates are serum albumins, keyhole limpet
30 hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid, and

other proteins well known to those of skill in the art. Compositions of the invention can also contain liquids or excipients, such as water, saline, glycerol, dextrose, ethanol, or the like, singly or in combination, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes can also be used as a carrier for a composition of the invention, such liposomes are described above.

If desired, co-stimulatory molecules which improve immunogen presentation to lymphocytes, such as B7-1 or B7-2, or cytokines such as GM-CSF, IL-2, and IL-12, can be included in a composition of the invention. Optionally, adjuvants can also be included in a composition. Adjuvants which can be used include, but are not limited to: (1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (PCT Publ. No. WO 90/14837), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing various amounts of MTP-PE), formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA), (b) SAF, containing 10% Squalene, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) RibiTM adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (DetoxTM); (3) saponin adjuvants, such as StimulonTM (Cambridge Bioscience, Worcester, MA) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes); (4) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (5) cytokines, such as interleukins (e.g., IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, *etc.*), interferons (e.g., gamma interferon), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), *etc.*; (6) detoxified mutants of a bacterial ADP-ribosylating toxin such as a cholera toxin (CT), a pertussis toxin (PT), or an *E. coli* heat-labile toxin (LT), particularly LT-K63, LT-R72, CT-S109, PT-K9/G129; see, e.g., WO 93/13302 and WO 92/19265; (7) other

substances that act as immunostimulating agents to enhance the effectiveness of the composition; and (8) microparticles with adsorbed macromolecules, as described in copending U.S. Patent Application Serial No. 09/285,855 (filed April 2, 1999) and international Patent Application Serial No. PCT/US99/17308 (filed July 29, 1999). Alum and MF59 are preferred. The effectiveness of an adjuvant can be determined by measuring the amount of antibodies directed against an immunogenic polypeptide containing an HCV antigenic sequence resulting from administration of this polypeptide in immunogenic compounds which are also comprised of the various adjuvants.

As mentioned above, muramyl peptides include, but are not limited to, N-acetylmuramyl-L-threonyl-D-isoglutamine (thr-MDP), -acetyl-normuramyl-L-alanyl-D-isoglutamine (CGP 11637, referred to as nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine (CGP 19835A, referred to as MTP-PE), *etc.*

Thus, such recombinant or synthetic HCV polypeptides can be used in vaccines and as diagnostics. Further, antibodies raised against these polypeptides can also be used as diagnostics, or for passive immunotherapy. In addition, antibodies to these polypeptides are useful for isolating and identifying HCV particles.

Native HCV antigens can also be isolated from HCV virions. The virions can be grown in HCV infected cells in tissue culture, or in an infected host.

Administration and Delivery

The polynucleotide and polypeptide compositions described herein (*e.g.*, immunogenic compounds) may be administered to a subject using any suitable delivery means. Methods of delivering nucleic acids into host cells are discussed above. Further, HCV polynucleotides and/or polypeptides can be administered parenterally, by injection, usually, subcutaneously, intramuscularly, transdermally or transcutaneously. Certain adjuvants, *e.g.* LTK63, LTR72 or PLG formulations, can be administered intranasally or orally. Additional formulations which are suitable for other modes of administration include suppositories. For suppositories, traditional binders and carriers can include, for example, polyalkylene glycols or triglycerides; such suppositories can be formed from

mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%. Other oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain 10%-95% of active ingredient, preferably 25%-70%.

The polypeptides of the present invention can be formulated into the immunogenic compound as neutral or salt forms. Pharmaceutically acceptable salts include the acid addition salts (formed with free amino groups of the peptide) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids such as acetic, oxalic, tartaric, maleic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

The immunogenic compounds are administered in a manner compatible with the dosage formulation, and in such amount as will be prophylactically and/or therapeutically effective. The quantity to be administered, which is generally in the range of 5 micrograms to 250 micrograms of polypeptide per dose, depends on the subject to be treated, capacity of the subject's immune system to synthesize antibodies, and the degree of protection desired. Precise amounts of active ingredient required to be administered may depend on the judgment of the practitioner and can be peculiar to each subject.

The immunogenic compound can be given in a single dose schedule, or preferably in a multiple dose schedule. A multiple dose schedule is one in which a primary course of vaccination can be with 1-10 separate doses, followed by other doses given at subsequent time intervals required to maintain and or reenforce the immune response, for example, at 1-4 months for a second dose, and if needed, a subsequent dose(s) after several months. Further, the course of administration may include polynucleotides and polypeptides, together or sequentially (for example, priming with a polynucleotide composition and boosting with a polypeptide composition). The dosage regimen will also, at least in part,

be determined by the need of the individual and be dependent upon the judgment of the practitioner.

In certain embodiments, administration of the polynucleotides and polypeptides described herein is used to activate T cells. In addition to the practical advantages of simplicity of construction and modification, administration of polynucleotides encoding mutant NS polypeptides results in the synthesis of a mutant NS polypeptide in the host. Thus, these immunogens are presented to the host immune system with native post-translational modifications, structure, and conformation. The polynucleotides are preferably injected intramuscularly to a large mammal, such as a human, at a dose of 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 5 or 10 mg/kg.

The proteins and/or polynucleotides can be administered either to a mammal which is not infected with an HCV or can be administered to an HCV-infected mammal. The particular dosages of the polynucleotides or fusion proteins in a composition or will depend on many factors including, but not limited to the species, age, and general condition of the mammal to which the composition is administered, and the mode of administration of the composition. An effective amount of the composition of the invention can be readily determined using only routine experimentation. *In vitro* and *in vivo* models can be employed to identify appropriate doses. Generally, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 5 or 10 mg will be administered to a large mammal, such as a baboon, chimpanzee, or human. If desired, co-stimulatory molecules or adjuvants can also be provided before, after, or together with the compositions.

Antibodies and Diagnostics

Antibodies, both monoclonal and polyclonal, which are directed against HCV epitopes are particularly useful in diagnosis, and those which are neutralizing are useful in passive immunotherapy. Monoclonal antibodies, in particular, may be used to raise anti-idiotypic antibodies.

Anti-idiotypic antibodies are immunoglobulins which carry an "internal image" of the antigen of the infectious agent against which protection is desired. Techniques for raising anti-idiotypic antibodies are known in the art. See, e.g., Grzych (1985), Nature

316:74; MacNamara et al. (1984), Science 226:1325, Uytdehaag et al (1985), J. Immunol. 134:1225. These anti-idiotypic antibodies may also be useful for treatment and/or diagnosis of NANBH, as well as for an elucidation of the immunogenic regions of HCV antigens.

An immunoassay for viral antigen may use, for example, a monoclonal antibody
5 directed towards a viral epitope, a combination of monoclonal antibodies directed towards epitopes of one viral polypeptide, monoclonal antibodies directed towards epitopes of different viral polypeptides, polyclonal antibodies directed towards the same viral antigen, polyclonal antibodies directed towards different viral antigens or a combination of monoclonal and polyclonal antibodies.

10 Immunoassay protocols may be based, for example, upon competition, or direct reaction, or sandwich type assays. Protocols may also, for example, use solid supports, or may be by immunoprecipitation. Most assays involve the use of labeled antibody or polypeptide. The labels may be, for example, fluorescent, chemiluminescent, radioactive, or dye molecules. Assays which amplify the signals from the probe are also known.

15 Examples of which are assays which utilize biotin and avidin, and enzyme-labeled and mediated immunoassays, such as ELISA assays.

An enzyme-linked immunosorbent assay (ELISA) can be used to measure either antigen or antibody concentrations. This method depends upon conjugation of an enzyme to either an antigen or an antibody, and uses the bound enzyme activity as a quantitative
20 label. To measure antibody, the known antigen is fixed to a solid phase (e.g., a microplate or plastic cup), incubated with test serum dilutions, washed, incubated with anti-immunoglobulin labeled with an enzyme, and washed again. Enzymes suitable for labeling are known in the art, and include, for example, horseradish peroxidase. Enzyme activity bound to the solid phase is measured by adding the specific substrate, and determining
25 product formation or substrate utilization colorimetrically. The enzyme activity bound is a direct function of the amount of antibody bound.

To measure antigen, a known specific antibody is fixed to the solid phase, the test material containing antigen is added, after an incubation the solid phase is washed, and a second enzyme-labeled antibody is added. After washing, substrate is added, and enzyme
30 activity is estimated colorimetrically, and related to antigen concentration.

The HCV fusion proteins, such as NS3 mutant and core fusion proteins, can also be used to produce HCV-specific polyclonal and monoclonal antibodies. HCV-specific polyclonal and monoclonal antibodies specifically bind to HCV antigens.

5 Polyclonal antibodies can be produced by administering the fusion protein to a mammal, such as a mouse, a rabbit, a goat, or a horse. Serum from the immunized animal is collected and the antibodies are purified from the plasma by, for example, precipitation with ammonium sulfate, followed by chromatography, preferably affinity chromatography. Techniques for producing and processing polyclonal antisera are known in the art.

10 Monoclonal antibodies directed against HCV-specific epitopes present in the fusion proteins can also be readily produced. Normal B cells from a mammal, such as a mouse, immunized with, e.g., a mutant NS3 polypeptide or NS-core fusion protein can be fused with, for example, HAT-sensitive mouse myeloma cells to produce hybridomas. Hybridomas producing HCV-specific antibodies can be identified using RIA or ELISA and isolated by cloning in semi-solid agar or by limiting dilution. Clones producing HCV-specific antibodies are isolated by another round of screening.

15 Antibodies, either monoclonal and polyclonal, which are directed against HCV epitopes, are particularly useful for detecting the presence of HCV or HCV antigens in a sample, such as a serum sample from an HCV-infected human. An immunoassay for an HCV antigen may utilize one antibody or several antibodies. An immunoassay for an HCV antigen may use, for example, a monoclonal antibody directed towards an HCV epitope, a combination of monoclonal antibodies directed towards epitopes of one HCV polypeptide, monoclonal antibodies directed towards epitopes of different HCV polypeptides, polyclonal antibodies directed towards the same HCV antigen, polyclonal antibodies directed towards different HCV antigens, or a combination of monoclonal and polyclonal antibodies. Immunoassay protocols may be based, for example, upon competition, direct reaction, or sandwich type assays using, for example, labeled antibody. The labels may be, for example, fluorescent, chemiluminescent, or radioactive.

25 The polyclonal or monoclonal antibodies may further be used to isolate HCV particles or antigens by immunoaffinity columns. The antibodies can be affixed to a solid support by, for example, adsorption or by covalent linkage so that the antibodies retain

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their immunoselective activity. Optionally, spacer groups may be included so that the antigen binding site of the antibody remains accessible. The immobilized antibodies can then be used to bind HCV particles or antigens from a biological sample, such as blood or plasma. The bound HCV particles or antigens are recovered from the column matrix by, for example, a change in pH.

Methods of Eliciting Immune Responses

HCV-specific T cells that are activated by the above-described polypeptides, expressed *in vivo* or *in vitro* preferably recognize an epitope of an HCV polypeptide such as a mutant NS3 polypeptide, including an epitope of a mutant HCV polypeptide. HCV-specific T cells can be CD8⁺ or CD4⁺.

HCV-specific CD8⁺ T cells preferably are cytotoxic T lymphocytes (CTL) which can kill HCV-infected cells that display NS3, NS4, NS5a, NS5b epitopes complexed with an MHC class I molecule. HCV-specific CD8⁺ T cells may also express interferon- γ (IFN- γ). HCV-specific CD8⁺ T cells can be detected by, for example, ⁵¹Cr release assays. ⁵¹Cr release assays measure the ability of HCV-specific CD8⁺ T cells to lyse target cells displaying a nonstructural (*e.g.*, mutant NS) epitope. HCV-specific CD8⁺ T cells which express IFN- γ can also be detected by immunological methods, preferably by intracellular staining for IFN- γ after *in vitro* stimulation with a mutant NS polypeptide.

HCV-specific CD4⁺ cells activated by the above-described polypeptides, expressed *in vivo* or *in vitro*, and combinations of the individual components of these proteins, preferably recognize an epitope of a mutant non-structural polypeptide, including an epitope of a mutant protein, that is bound to an MHC class II molecule on an HCV-infected cell and proliferate in response to stimulating mutant peptides.

HCV-specific CD4⁺ T cells can be detected by a lymphoproliferation assay. Lymphoproliferation assays measure the ability of HCV-specific CD4⁺ T cells to proliferate in response to an epitope.

Mutant NS (or fusions thereof with core, envelope or other viral polypeptides) can be used to activate HCV-specific T cells either *in vitro* or *in vivo*. Activation of HCV-specific T cells can be used, *inter alia*, to provide model systems to optimize CTL

responses to HCV and to provide prophylactic or therapeutic treatment against HCV infection. For *in vitro* activation, proteins are preferably supplied to T cells via a plasmid or a viral vector, such as an adenovirus vector, as described above.

5 Polyclonal populations of T cells can be derived from the blood, and preferably from peripheral lymphoid organs, such as lymph nodes, spleen, or thymus, of mammals that have been infected with an HCV. Preferred mammals include mice, chimpanzees, baboons, and humans. The HCV serves to expand the number of activated HCV-specific T cells in the mammal. The HCV-specific T cells derived from the mammal can then be restimulated *in vitro* by adding HCV epitopic peptides to the T cells. The HCV-specific T
10 cells can then be tested for, *inter alia*, proliferation (*e.g.*, lymphoproliferation assays known in the art), the production of IFN- γ , and the ability to lyse target cells displaying HCV NS epitopes *in vitro*.

The following examples are meant to illustrate the invention and are not meant to
15 limit it in any way. Those of ordinary skill in the art will recognize modifications within the spirit and scope of the invention as set forth herein.

EXAMPLES

Example 1: Constructs

pCMV-II: pCMV-II (Figure 7, SEQ ID NO:5) was created to contain the human
5 CMV promoter, enhancer, intron A, polylinker and the bovine growth hormone terminator
in a deleted-pUC backbone (Life Technologies).

pT7-HCV: pT7-HCV was created in a polylinker-modified pUC vector to contain
full-length HCV cDNA preceded by a synthetic T7 promoter. pT7-HCV also contains the
complete 5' UTR and the poly A version of the 3' UTR.

10 pCMV.ΔNS35: To generate pCMV.ΔNS35 (Figure 5, SEQ ID NO:3), a two step
procedure was undertaken. First, a PCR product was generated from pT7-HCV that
corresponded to the following: a 5' EcoRI site, followed by the Kozak sequence of
ACCATGG; the initiator ATG followed by amino acid #1242 and continuing to the StuI
site. Second, the StuI to XbaI fragment from a full-length genomic clone was isolated.
15 The genomic clone consisted of the T7 promoter fused to the full-length HCV cDNA with
the poly A version of the 3' end, in a pUC vector. Finally, the EcoRI-StuI and StuI-XbaI
fragments were ligated into the pCMV-II expression vector, transformed into HB101
competent cells and plated onto ampicillin (100 µg/ml). Miniprep analyses led to the
identification of the desired clone which was amplified on a larger scale using a Quigen
20 Gigaprep kit following the manufacturer's specifications. The resulting clone was named
pCMV.ΔNS35 (Figure 5, SEQ ID NO:3).

pd.ΔNS3NS5: As shown schematically in Figure 10, the yeast expression plasmid
pd.ΔNS3NS5 (SEQ ID NO:8) was constructed using restriction fragments obtained from
the mammalian expression plasmid pCMV.KM.ΔNS35. pCMV.KM.ΔNS35 is identical to
25 pCMV.ΔNS35 (Figure 5, SEQ ID NO:3) except that it contains a kanamycin resistance
gene in the viral backbone. pCMV.KM.ΔNS35 was digested with EcoRI and NheI to
obtain 2895bp EcoRI-NheI fragment. EcoRI-NheI fragment was ligated into pRSET
HindIII-NheI subcloning vector with oligos (HE) from HindIII to EcoRI. After sequence
verification, pRSETHindIII-NheI #6 was digested with HindIII and NheI to obtain a

2908bp HindIII-NheI fragment.

pCMV.KM.ΔNS35 was linearized with XbaI and ligated with synthetic oligos (XS) from XbaI-SalI. The ligation was digested with NheI and SalI to obtain 2481bp NheI-SalI fragment. The fragment was ligated into pET3a NheI-SalI subcloning vector. After
5 sequence verification, pET3a NheI-SalI #2 was digested with NheI and SalI to obtain a 2481bp NheI-SalI fragment. BamHI-HindIII ADH2/GAPDH promoter fragment was then ligated with HindIII-NheI and NheI-SalI fragments into pBS24.1 BamHI-SalI yeast expression vector.

pd.ΔNS3NS5.PJ: pd.ΔNS3NS5.PJ (Figures 13 and 14; SEQ ID NO:10) was
10 generated to create a "perfect junction" at the 5' and 3' end of the HCV coding region. At the 5' end of pd.ΔNS3NS5, there were 6 extra bases between the yeast ADH2/GAPDH promoter and the ATG of the polypeptide. At the 3' end, there were 52 bases of untranslated sequence between the stop codon of the polypeptide and the α-factor terminator in the yeast expression vector. pd.ΔNS3NS5.PJ was created by digesting
15 pd.ΔNS3NS5 #17 with ScaI and SphI to obtain 4963bp ScaI-SphI fragment. pd.NS5b3011 was digested with SphI and SalI to obtain a 321bp SphI-SalI fragment which gave the "perfect junction" at the 3' end of the polypeptide. The ScaI-SphI and SphI-SalI fragments were ligated into pSP72 HindIII-SalI subcloning vector with synthetic oligos from HindIII-ScaI(HS) for the "perfect junction" at the 5' end.

20 The region of synthetic sequence in pSP72 HindIII-SalI clone# 6 was verified. pSP72 HindIII-SalI clone#6 was digested with HindIII and BlnI or with BlnI and SalI to obtain 2441bp HindIII-BlnI and 2895bp BlnI-SalI fragments, respectively. The BamHI-HindIII ADH2/GAPDH promoter fragment was ligated to HindIII-BlnI and BlnI-SalI fragments into pBS24.1 BamHI-SalI yeast expression vector.

25 pd.ΔNS3NS5.PJ.core121RT and pd.ΔNS3NS5.PJ.core173RT were generated and encode HCV core aa 1-121 at the C-terminus of the ΔNS3NS5 polypeptide (designated pd.ΔNS3NS5.PJ.core121RT, SEQ ID NO:12) and core aa 1-173 at the C-terminus of the ΔNS3NS5 polypeptide (designated pd.ΔNS3NS5.PJ.core173RT, SEQ ID NO:14). The core sequence had aa 9 mutated from Lys to Arg and aa 11 mutated from Asn to Thr,

designated as core 121RT or 173RT.

5 pd.ΔNS3NS5.PJ.core121RT and pd.ΔNS3NS5.PJ.core173RT: To generate
pd.ΔNS3NS5.PJ.core121RT (Figure 17, SEQ ID NO:12) and pd.ΔNS3NS5.PJ.core173RT
(Figure 18, SEQ ID NO:14). As shown in Figure 16, a NotI-Sal HCVcore121RT and
HCVcore173RT were amplified by PCR, from an *E. coli* expression plasmid,
pSODCF2.HCVcore191RT #2. Either the core 121RT Not-SalI PCR product or the core
173RT Not-SalI PCR product were ligated into a pT7Blue2 PstI-SalI subcloning vector
with synthetic oligos (PN) from PstI to NotI. After sequence confirmation,
pT7Blue2core121RT clone#9 and pT7Blue2core173RT clone#11 was digested with PstI
10 and SalI to obtain 403bp and 559bp PstI-SalI fragments, respectively, for further cloning.

A 121bp NotI-PstI fragment from pSP72 HindIII-SalI clone #6 was isolated as
described above during the cloning of pd.ΔNS3NS5.PJ. NotI-PstI and PstI-SalI fragments
were assembled into a vector made by digesting pd.ΔNS3NS5.PJ clone#5 (described above)
with NotI and SalI.

15 ΔNS3NS5 and Core 140 and Core 150: An HCV core epitope was found which
elicits CTLs in baboons (HCV core aa 121-135). Since pd.ΔNS3NS5.PJ.core121RT ends
right before this potentially important epitope and was expressed better than the longer
pd.ΔNS3NS5.PJ.core173RT construct (Example 2), two intermediate constructs were
made which include this epitope, possibly giving intermediate expression levels. The two
20 new constructs fused HCV core aa 1-140 or HCV core aa1-150 to the C terminus of
ΔNS3NS5.PJ.

pd.ΔNS3NS5.PJ.core140RT (Figure 21, SEQ ID NO:16) and
pd.ΔNS3NS5.PJ.core150RT (Figure 22, SEQ ID NO:18): As shown in Figure 20, a PstI-
SalI HCVcore140RT and a PstI-SalIHCVcore150RT fragment were amplified by PCR
25 from pd.ΔNS3NS5.PJ.core173RT clone #16. Ligate either HCV core PstI-SalI PCR
products into pT7Blue2 PstI-SalI subcloning vector. After sequence confirmation,
pT7Blue2core140RT clone#22 and pT7Blue2core150RT clone#26 were digested with
PstI-SalI to obtain 460bp and 490bp PstI-SalI fragments, respectively, for further cloning.

A 121bp NotI-PstI fragment was isolated from pSP72 HindIII-SalI clone #6 (as described above during the cloning of pd.ΔNS3NS5.PJ. NotI-PstI and PstI-SalI fragments were assembled into a vector made by digesting pd.ΔNS3NS5.PJ clone#5 (described above) with NotI and SalI.

5

Example 2: Protein Expression

Various of the constructs described herein, encoding HCV-1 ΔNS3 to NS5 antigen (aa 1242-3011), were expressed in yeast. *S. cerevisiae* strain AD3 was transformed with pd.ΔNS3NS5 and checked for expression. A stained protein band at the expected
10 molecular weight of 194 kD was not observed (Figure 12). Strain AD3 was also transformed with pd.ΔNS3NS5.PJ clone #5 and checked for expression. A protein band of the expected molecular weight of 194kD was detected (Figure 15). Strain AD3 was transformed with pd.ΔNS3NS5.PJ.core121RT clone #6 and pd.ΔNS3NS5.PJ.core173RT clone#15 and checked for expression. Protein bands of the expected molecular weight of
15 206kD and 210kD, respectively, were observed. Expression levels of the pd.ΔNS3NS5.PJ.core173RT construct were much less than that of the pd.ΔNS3NS5.PJ.core121RT construct. (See Figure19). Thus, there is a correlation of protein expression levels and the length of HCV core.

Strain AD3 were transformed with pd.ΔNS3NS5.PJ.core140RT clone# 29 and
20 pd.ΔNS3NS5.PJ.core150RT clone#35 and checked for expression. Bands of the expected molecular weights of 208kD and 209kD were seen by stain at levels close to those of pd.ΔNS3NS5core173RT (Figure 23).

Example 3: Eliciting Immune Responses

25 A. Immunization

To evaluate the immunogenicity of the mutant NS polypeptides, studies using guinea pigs, rabbits, mice, rhesus macaques and/or baboons are performed. The studies are structured as follows: DNA immunization alone (single or multiple); DNA immunization followed by protein immunization (boost); DNA immunization followed by protein

immunization; immunization by PLG particles. Immunization is intramuscular or mucosally.

B. Humoral Immune Response

5 The humoral immune response is checked in serum specimens from immunized animals with anti-NS antibody ELISAs (enzyme-linked immunosorbent assays) at various times post-immunization. Briefly, serum from immunized animals is screened for antibodies directed against the NS or mutant NS proteins. Wells of ELISA microtiter plates are coated overnight with the selected HCV protein and washed four times; subsequently, blocking is done with PBS-0.2% Tween (Sigma). After removal of the blocking solution, diluted mouse serum is added. Sera are tested at various dilutions. Microtiter plates are washed and incubated with a secondary, peroxidase-coupled anti-mouse IgG antibody (Pierce, Rockford, IL). ELISA plates are washed and 3, 3', 5, 5'-tetramethyl benzidine (TMB; Pierce) is added per well. The optical density of each well is measured. Titers are typically reported as the reciprocal of the dilution of serum that gave a half-maximum optical density (O.D.). Similarly, generation of neutralization of binding (NOB) antibodies can be measured by methods known in the art.

C. Cellular Immune Response

20 The frequency of specific cytotoxic T-lymphocytes (CTL) is evaluated by a standard chromium release assay of peptide pulsed Balb/c mouse CD4 cells. Briefly, spleen cells (Effector cells, E) are obtained from the BALB/c mice immunized, cultured, restimulated, and assayed for CTL activity against HCV peptide-pulsed target cells. Cytotoxic activity is measured in a standard ⁵¹Cr release assay.

25

Example 4: Immunization with PLG-delivered DNA.

 The polylactide-co-glycolide (PLG) polymers are obtained from Boehringer Ingelheim, U.S.A. The PLG polymer is RG505, which has a copolymer ratio of 50/50 and a molecular weight of 65 kDa (manufacturers data). Cationic microparticles with adsorbed DNA are prepared using a modified solvent evaporation process, essentially as described in

30

Singh et al., *Proc. Natl. Acad. Sci. USA* (2000) 97:811-816. Briefly, the microparticles are prepared by emulsifying a 5% w/v polymer solution in methylene chloride with PBS at high speed using an IKA homogenizer. The primary emulsion is then added to distilled water containing cetyl trimethyl ammonium bromide (CTAB) (0.5% w/v). This results in the formation of a w/o/w emulsion which was stirred at room temperature, allowing the methylene chloride to evaporate. The resulting microparticles are washed in distilled water by centrifugation and freeze dried. Following preparation, washing and collection, DNA is adsorbed onto the microparticles by incubating cationic microparticles in a solution of DNA. The microparticles are then separated by centrifugation, the pellet washed with TE buffer and the microparticles are freeze dried, resuspended and administered to animals. Antibody titers are measured by ELISA assays.

All patents, patent applications, and other publications mentioned herein, are hereby incorporated herein by reference in their entireties.

What is claimed is:

1. An isolated mutant non-structural ("NS") HCV polypeptide comprising a polypeptide having a mutation in the catalytic domain of NS3, wherein said mutation functionally disrupts the catalytic domain.
- 5 2. The polypeptide of claim 1, wherein the mutation comprises a deletion.
3. The polypeptide of claim 1, wherein the mutation comprises a substitution.
- 10 4. The polypeptide of claim 1, wherein said NS polypeptide comprises NS3, NS4 and NS5.
5. The polypeptide of claim 1, wherein said NS polypeptide consists of NS3, NS4 and NS5.
- 15 6. The polypeptide of claim 1, wherein said NS polypeptide consists of NS3 and NS5.
7. The polypeptide of claim 6, wherein NS5 consists of NS5a.
- 20 8. The polypeptide of claim 6, wherein NS5 consists of NS5b.
9. The polypeptide of claim 1, wherein said NS polypeptide consists of NS3 and NS4.
- 25 10. The polypeptide of claim 9, wherein NS4 consists of NS4a.
11. The polypeptide of claim 9, wherein NS4 consists of NS4b.

12. The polypeptide of claim 4, further comprising a second viral polypeptide that is not NS3, NS4, or NS5 of HCV.

5 13. The polypeptide of claim 12, wherein the second viral polypeptide comprises an HCV Core polypeptide ("C"), or fragment thereof.

14. The polypeptide of claim 13, wherein the C polypeptide is truncated.

10 15. The polypeptide of claim 14, wherein the truncation is at amino acid 121.

16. The polypeptide of claim 12, wherein the polypeptide further comprises an HCV envelope protein ("E").

15 17. The polypeptide of claim 16, wherein the E is E1.

18. The polypeptide of claim 16, wherein the E is E2.

20 19. A composition comprising
(a) the polypeptide of claim 1; and
(b) a pharmaceutically acceptable excipient.

20. An isolated and purified polynucleotide which encodes the mutant HCV polypeptide according to claim 1.

25 21. A composition comprising
(a) the isolated purified polynucleotide of claim 20; and
(b) a pharmaceutically acceptable excipient.

30 22. The composition of claim 21, wherein the polynucleotide is DNA.

23. The composition of claim 21, wherein the polynucleotide is in a plasmid.
24. An expression vector comprising the polynucleotide of claim 20.
- 5 25. An expression vector comprising the polynucleotide of SEQ ID NO:8.
26. A host cell comprising the polynucleotide of claim 20.
27. The host cell of claim 26, wherein the cell is a yeast cell.
- 10 28. The host cell of claim 26, wherein the cell is a mammalian cell.
29. The host cell of claim 26, wherein the cell is an insect cell.
- 15 30. The host cell of claim 26, wherein the cell is a plant cell.
31. The host cell of claim 26, wherein the polynucleotide comprises the sequence of SEQ ID NO:8.
- 20 32. The polypeptide of claim 1, wherein the polypeptide further comprises SEQ ID NO:9.
33. A method of preparing a mutant NS HCV polypeptide, wherein the method comprises the steps of:
 - 25 a. transforming a host cell with an expression vector according to claim 24, under conditions wherein the polypeptide is expressed; and
 - 30 b. isolating the polypeptide.

34. The method of claim 33, wherein the host cell is a yeast cell.
35. The method of claim 33, wherein the host cell is a mammalian cell.
- 5 36. The method of claim 33, wherein the host cell is an insect cell.
37. The method of claim 33, wherein the host cell is a plant cell.
38. An antibody that specifically binds to a polypeptide of claim 1.
- 10 39. The antibody of claim 38, wherein the antibody is a monoclonal antibody.
40. The antibody of claim 38, wherein the antibody is a purified polyclonal antibody.
- 15 41. A method of eliciting an immune response in a subject, comprising the step of administering to the subject a polypeptide of claim 1.
42. A method of eliciting an immune response in a subject, comprising the step of administering to the subject a polynucleotide of claim 20.
- 20

ABSTRACT

Polypeptides comprising a mutant non-structural Hepatitis C virus useful in diagnostic and/or immunogenic compositions are disclosed, in which the mutant is an N-terminal mutation that functionally disrupt the catalytic domain of NS3. Polynucleotides encoding these polypeptides, host cells transformed with polynucleotides and methods of using the polypeptides and polynucleotides are also disclosed.

Cloning Scheme for Generating pCMV-NS35

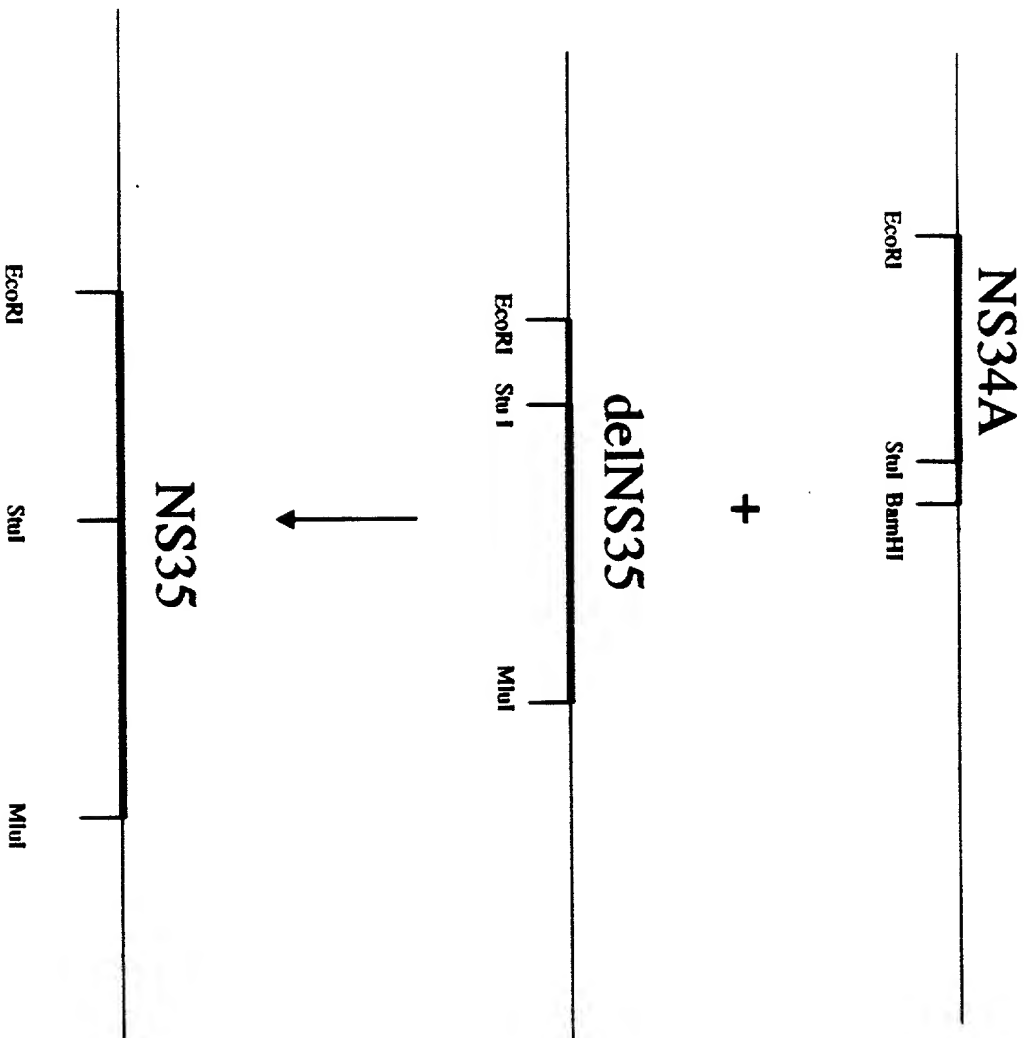
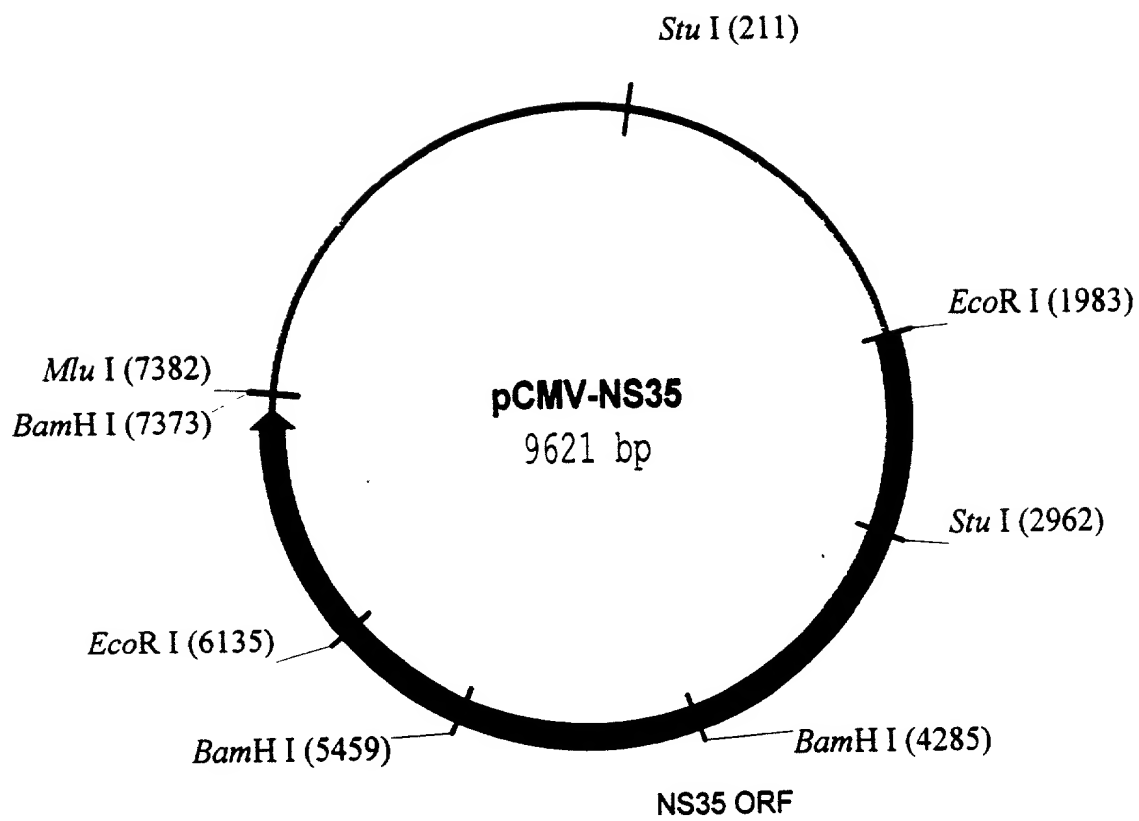


FIGURE 1

FIGURE 2



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1	TCGCGCGT	CGGTGATG	GGTGAAAACC	TCTGACACAT	GCAGCTCCCG	GAGACGGTCA	CAGCTTGTCT	GTAAGCGGAT
	AGCGCGCAAA	GCCACTACTG	CCACTTTTGG	AGACTGTGTA	CGTCGAGGGC	CTCTGCCAGT	GTCGAACAGA	CATTGCGCTA
81	GCCGGGAGCA	GACAAGCCCG	TCAGGGCGCG	TCAGCGGGTG	TTGGCGGGTG	TCGGGGCTGG	CTTAACATATG	CGGCATCAGA
	CGGCCCTCGT	CTGTTCGGGC	AGTCCCGCGC	AGTCGCCAC	AACCGCCAC	AGCCCCGACC	GAATTGATAC	GCCGTAGTCT
					StuI	~~~~~		
161	GCAGATTGTA	CTGAGAGTGC	ACCATATGAA	GCTTTTTGCA	AAAGCCTAGG	CCTCCAAAAA	AGCCTCCTCA	CTACTTCTGG
	CGTCTAACAT	GACTCTCAGC	TGGTATACTT	CGAAAAACGT	TTTCGGATCC	GGAGGTTTTT	TCGGAGGAGT	GATGAAGAC
241	AATAGCTCAG	AGGCCGAGGC	GGCCTCGGCC	TCTGCATAAA	TAAAAAAAT	TAGTCAGCCA	TGGGGCGGAG	AATGGGCGGA
	TTATCGAGTC	TCCGGCTCCG	CCGGAGCCGG	AGACGTATTT	ATTTTTTTTA	ATCAGTCGGT	ACCCCGCCTC	TTACCCGCCT
321	ACTGGGCGGG	GAGGGAATTA	TTGGCTATTG	GCCATTGCAT	ACGTTGTATC	TATATCATAA	TATGTACATT	TATATTGGCT
	TGACCCGCC	CTCCCTTAAT	AACCAGATAAC	CGGTAACGTA	TGCAACATAG	ATATAGTATT	ATACATGTAA	ATATAACCGA
401	CATGTCCAAT	ATGACCGCCA	TGTTGACATT	GATTATTGAC	TAGTTATTAA	TAGTAATCAA	TTACGGGGTC	ATTAGTTTAT
	GTACAGGTTA	TACTGGCGGT	ACAACGTGTA	CTAATAACTG	ATCAATAATT	ATCATTAGTT	AATGCCCCAG	TAATCAAGTA
481	AGCCCATATA	TGGAGTTCGG	CGTTACATAA	CTTACGGTAA	ATGGCCCCGC	TGGCTGACCG	CCCAACGACC	CCCGCCCAT
	TCGGGTATAT	ACCTCAAGGC	GCAATGTATT	GAATGCCATT	TACCGGGCGG	ACCGACTGGC	GGGTTGCTGG	GGGCGGGTAA
561	GACGTCAATA	ATGACGTATG	TTCCCATAGT	AACGCCAATA	GGGACTTTCC	ATTGACGTCA	ATGGGTGGAG	TATTTACGGT
	CTGCAGTTAT	TACTGCATAC	AAGGGTATCA	TTGCGGTTAT	CCCTGAAAGG	TAAGTGCAGT	TACCCACCTC	ATAAATGCCA
641	AAACTGCCCA	CTTGGCAGTA	CATCAAGTGT	ATCATATGCC	AAGTCCGCCC	CCTATTGACG	TCAATGACGG	TAAATGGCCC
	TTTGACGGGT	GAACCGTCAT	GTAGTTCACA	TAGTATACGG	TTCAGGCGGG	GGATAACTGC	AGTTACTGCC	ATTTACGGGG
721	GCCTGGCATT	ATGCCCAGTA	CATGACCTTA	CGGGACTTTC	CTACTTGGCA	GTACATCTAC	GTATTAGTCA	TCGCTATTAC
	CGGACCGTAA	TACGGGTCAT	GTACTGGAAT	GCCCTGAAAG	GATGAACCGT	CATGTAGATG	CATAATCAGT	AGCGATAATG
801	CATGGTGATG	CGGTTTTTGGC	AGTACACCAA	TGGGCGTGGA	TAGCGGTTTG	ACTCACGGGG	ATTTCCAAGT	CTCCACCCCA
	GTACCACTAC	GCCAAAACCG	TCATGTGGTT	ACCCGCACCT	ATCGCCAAAC	TGAGTGCCCC	TAAAGGTTCA	GAGGTGGGGT
881	TTGACGTCAA	TGGGAGTTTG	TTTTGGCACC	AAAATCAACG	GGACTTTCCA	AAATGTGCTA	ATAACCCCGC	CCCGTTGACG
	AACTGCAGTT	ACCCTCAAAC	AAAACCGTGG	TTTTAGTTGC	CCTGAAAGGT	TTTACAGCAT	TATTGGGGCG	GGGCAACTGC
961	CAAATGGGCG	GTAGGCGTGT	ACGGTGGGAG	GTCTATATAA	GCAGAGCTCG	TTTAGTGAAC	CGTCAGATCG	CCTGGAGACG
	GTTTACCCGC	CATCCGCACA	TGCCACCCTC	CAGATATATT	CGTCTCGAGC	AAATCACTTG	GCAGTCTAGC	GGACCTCTGC
1041	CCATCCACGC	TGTTTTGACC	TCCATAGAAG	ACACCGGGAC	CGATCCAGCC	TCCGCGGGCG	GGAACGGTGC	ATTGGAACGC
	GGTAGGTGCG	ACAAAACCTGG	AGGTATCTTC	TGTGGCCCTG	GCTAGGTCGG	AGGCGCCGGC	CCTTGCCACG	TAACCTTGCG
1121	GGATTCCCGG	TGCCAAGAGT	GACGTAAGTA	CCGCCTATAG	ACTCTATAGG	CACACCCCTT	TGGCTCTTAT	GCATGCTATA
	CCTAAGGGGC	ACGGTTCTCA	CTGCATTTCAT	GGCGGATATC	TGAGATATCC	GTGTGGGGAA	ACCGAGAATA	CGTACGATAT
1201	CTGTTTTTGG	CTTGGGGCCT	ATACACCCCC	GCTCCTTATG	CTATAGGTGA	TGGTATAGCT	TAGCCTATAG	GTGTGGGGTA
	GACAAAAACC	GAACCCCGGA	TATGTGGGGG	CGAGGAATAC	GATATCCACT	ACCATATCGA	ATCGGATATC	CACACCCAAT
1281	TTGACCATT	TTGACCACTC	CCCTATTGGT	GACGATACTT	TCCATTACTA	ATCCATAACA	TGGCTCTTTG	CCACAACCTAT
	AACTGGTAAT	AACTGGTGAG	GGGATAACCA	CTGCTATGAA	AGGTAATGAT	TAGGTATTGT	ACCGAGAAAC	GGTGTGTGATA
1361	CTCTATTGGC	TATATGCCAA	TACTCTGTCC	TTCAGAGACT	GACACGGACT	CTGTATTTTT	ACAGGATGGG	GTCCATTTAT
	GAGATAACCG	ATATACGGTT	ATGAGACAGG	AAGTCTCTGA	CTGTGCCTGA	GACATAAAAA	TGTCTTACCC	CAGGTAATAA

FIGURE 3 - Page 2

1441 TATTTACAAA TTCACATATA CAACAACGCC GTCCCCCGTG CCCGCGAGTTT TTATTAAACA TAGCGTGGGA TCTCCGACAT
ATAAATGTTT AAGTGTATAT GTTGTTCGG CAGGGGGCAC GGGCGTCAAA AATAATTTGT ATCGCACCTT AGAGGCTGTA

1521 CTCGGGTACG TGTTCCGGAC ATGGGCTCTT CTCCGGTAGC GGCGGAGCTT CCACATCCGA GCCCTGGTCC CATCCGTCCA
GAGCCCATGC ACAAGGCCTG TACCCGAGAA GAGGCCATCG CCGCCTCGAA GGTGTAGGCT CGGGACCAGG GTAGGACAGT

1601 GCGGCTCATG GTCGCTCGGC AGCTCCTTGC TCCTAACAGT GGAGGCCAGA CTTAGGCACA GCACAATGCC CACCACCACC
CGCCGAGTAC CAGCGAGCCG TCGAGGAACG AGGATTGTCA CCTCCGGTCT GAATCCGTGT CGTGTTACGG GTGGTGGTGG

1681 AGTGTGCCGC ACAAGGCCGT GGCGGTAGGG TATGTGTCTG AAAATGAGCT CGGAGATTGG GCTCGCACCT GGACGCAGAT
TCACACGGCG TGTTCCGGCA CCGCCATCCC ATACACAGAC TTTTACTCGA GCCTCTAACC CGAGCGTGGG CCTGCGTCTA

1761 GGAAGACTTA AGGCAGCGGC AGAAGAAGAT GCAGGCAGCT GAGTTGTGTG ATTCTGATAA GAGTCAGAGG TAACTCCCGT
CCTTCTGAAT TCCGTCGCCG TCTTCTTCTA CGTCCGTCGA CTCAACAACA TAAGACTATT CTCAGTCTCC ATTGAGGGCA

1841 TGCGGTGCTG TTAACGGTGG AGGGCAGTGT AGTCTGAGCA GTACTCGTTG CTGCCGCGCG CGCCACCAGA CATAATAGCT
ACGCCACGAC AATTGCCACC TCCCGTCACA TCAGACTCGT CATGAGCAAC GACGGCGCGC GCGGTGGTCT GTATTATCGA

+2 EcoRI M A A
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1921 GACAGACTAA CAGACTGTTC CTTTCCATGG GTCTTTTCTG CAGTCACCGT CGTCGACCTA AGAATTCACC ATGGCTGCAT  
CTGTCTGATT GTCTGACAAG GAAAGGTACC CAGAAAAGAC GTCAGTGGCA GCAGCTGGAT TCTTAAGTGG TACCGACGTA

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+2 Y A A Q G Y K V L V L N P S V A A T L G F G A Y M S K  
2001 ATGCAGCTCA GGGCTATAAG GTGCTAGTAC TCAACCCCTC TGTTGCTGCA AACTGGGCT TTGGTGCTTA CATGTCCAAG  
TACGTCGAGT CCCGATATTC CACGATCATG AGTTGGGGAG ACAACGACGT TGTGACCCGA AACCACGAAT GTACAGGTTC

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+2 A H G I D P N I R T G V R T I T T G S P I T Y S T Y G  
2081 GCTCATGGGA TCGATCCTAA CATCAGGACC GGGGTGAGAA CAATTACCAC TGGCAGCCCC ATCAGCTACT CCACCTACGG  
CGAGTACCTT AGCTAGGATT GTAGTCTCTG CCCCCTCTT GTTAATGGTG ACCGTCGGGG TAGTGATGA GGTGGATGCC

---

+2 K F L A D G G C S G G A Y D I I I C D E C H S T D A  
2161 CAAGTTCCTT GCCGACGGCG GGTGCTCGGG GGGCGCTTAT GACATAATAA TTTGTGACGA GTGCCACTCC ACGGATGCCA  
GTTCAAGGAA CGGCTGCCGC CCACGAGCCC CCCGGAATA CTGTATTATT AAACACTGCT CACGGTGAGG TGCCTACGGT

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+2 T S I L G I G T V L D Q A E T A G A R L V V L A T A T  
2241 CATCATCTT GGGCATTGGC ACTGTCCTTG ACCAAGCAGA GACTGCGGG GCGAGACTGG TTGTGCTCGC CACCGCCACC  
GTAGGTAGAA CCCGTAACCG TGACAGGAAC TGGTTCGTCT CTGACGCCCC CGCTCTGACC AACACGAGCG GTGGCGGTGG

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+2 P P G S V T V P H P N I E E V A L S T T G E I P F Y G  
2321 CCTCCGGGCT CCGTCACTGT GCGCCATCCC AACATCGAGG AGGTGTCTCT GTCCACCACC GGAGAGATCC CTTTTTACGG  
GGAGGCCCGA GGCAGTGACA CGGGGTAGGG TTGTAGCTCC TCCAACGAGA CAGGTGGTGG CCTCTCTAGG GAAAAATGCC

---

+2 K A I P L E V I K G G R H L I F C H S K K K C D E L  
2401 CAAGGCTATC CCCCTCGAAG TAATCAAGGG GGGGAGACAT CTCATCTTCT GTCATTCAA GAAGAAGTGC GACGAAGTGC  
GTTCCGATAG GGGGAGCTTC ATTAGTTCCC CCCCTCTGTA GAGTAGAAGA CAGTAAGTTT CTTGTTTACG CTGCTTGAGC

---

+2 A A K L V A L G I N A V A Y Y R G L D V S V I P T S G  
2481 CCGCAAAGCT GGTGCGATTG GGCATCAATG CCGTGGCCTA CTACCGCGGT CTTGACGTGT CCGTCATCCC GACCAGCGGC  
GGCGTTTCGA CCAGCGTAAC CCGTAGTTAC GGCACCGGAT GATGGCGCCA GAAGTGACA GGCAGTAGGG CTGGTGGCGG

---

+2 D V V V V A T D A L M T G Y T G D F D S V I D C N T C  
2561 GATGTTGTCG TCGTGGAAC CGATGCCCTC ATGACCGGCT ATACCGGCGA CTTGACTCG GTGATAGACT GCAATACGTG  
CTACAACAGC AGCACCGTTG GCTACGGGAG TACTGGCCGA TATGGCCGCT GAAGCTGAGC CACTATCTGA CGTTATGCAC

DDBJ/EMBL/GenBank

## FIGURE 3 - Page 3

+2 V T Q T V D F S L D P T F T I E T I T L P Q D A V S  
 2641 . TGTCACCCAG ACAGTCGATT TCAGCCTTGA CCCTACCTTC ACCATTGAGA CAATCACGCT CCCCCAAGAT GCTGTCTCCC  
 ACAGTGGGTC TGTCAGCTAA AGTCGGAAGT GGGATGGAAG TGGTAACTCT GTTAGTGCGA GGGGGTCTA CGACAGAGGG

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+2 R T Q R R G R T G R G K P G I Y R F V A P G E R P S G  
 2721 GCACTCAACG TCGGGGAGG ACTGGCAGGG GGAAGCCAGG CATCTACAGA TTTGTGGCAG CGGGGGAGCG CCCCTCCGGC  
 CGTGAGTTGC AGCCCCGTCC TGACCGTCCC CTTTCGGTCC GTAGATGTCT AAACACCGTG GCCCCCTCGC GGGGAGGCCG

---

+2 M F D S S V L C E C Y D A G C A W Y E L T P A E T T V  
 2801 ATGTTCTGACT CGTCCGTCCT CTGTGAGTGC TATGACGCAG GCTGTGCTTG GTATGAGCTC ACGCCCGCCG AGACTACAGT  
 TACAAGCTGA GCAGGCAGGA GACACTCACG ATACTGCGTC CGACACGAAC CATACTCGAG TGCGGGCGGC TCTGATGTCA

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+2 R L R A Y M N T P G L P V C Q D H L E F W E G V F T  
 2881 TAGGCTACGA GCGTACATGA ACACCCCGGG GCTTCCCGTG TGCCAGGACC ATCTTGAATT TTGGGAGGGC GTCTTTACAG  
 ATCCGATGCT CGCATGTACT TGTGGGGCCC CGAAGGGCAC ACGGTCCTGG TAGAACTTAA AACCTCCCG CAGAAATGTC

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+2 G L T H I D A H F L S Q T K Q S G E N L P Y L V A Y Q  
 StuI  
 ~~~~  
 2961 GCCTCACTCA TATAGATGCC CACTTTCTAT CCCAGACAAA GCAGAGTGGG GAGAACCCTC CTTACCTGGT AGCGTACCAA
 CGGAGTGAGT ATATCTACGG GTGAAAGATA GGGTCTGTTT CGTCTCACCC CTCTTGGAAG GAATGGACCA TCGCATGTTT

+2 A T V C A R A Q A P P P S W D Q M W K C L I R L K P T
 3041 GCCACCGTGT GCGCTAGGGC TCAAGCCCCT CCCCCATCGT GGGACCAGAT GTGGAAGTGT TTGATTCGCC TCAAGCCAC
 CGGTGGCACA CGCGATCCCG AGTTCGGGGA GGGGGTAGCA CCCTGGTCTA CACCTTCACA AACTAAGCGG AGTTCGGGTG

+2 L H G P T P L L Y R L G A V Q N E I T L T H P V T K
 3121 CCTCCATGGG CCAACACCCC TGCTATACAG ACTGGGCGCT GTTCAGAATG AAATCACCTC GACGCACCCA GTCACCAAAT
 GGAGGTACCC GGTGTGGGG ACGATATGTC TGACCCCGCA CAAGTCTTAC TTAGTGGGA CTGCGTGGGT CAGTGGTTTA

+2 Y I M T C M S A D L E V V T S T W V L V G G V L A A L
 3201 ACATCATGAC ATGCATGTCG GCGACCTGG AGGTCGTCAC GAGCACCTGG GTGCTCGTTG GCGGCGTCCT GGCTGCTTTG
 TGTAGTACTG TACGTACAGC CGGCTGGACC TCCAGCAGTG CTCGTGGACC CACGAGCAAC CGCCGAGGA CCGACGAAAC

+2 A A Y C L S T G C V V I V G R V V L S G K P A I I P D
 3281 GCCGCGTATT GCCTGTCAAC AGGCTGCGTG GTCATAGTGG GCAGGGTCGT CTGTCCGGG AAGCCGGCAA TCATACCTGA
 CGGCGCATAA CGGACAGTTG TCCGACGCAC CAGTATCACC CGTCCAGCA GAACAGGCC TCGGCCGTT AGTATGACT

+2 R E V L Y R E F D E M E E C S Q H L P Y I E Q G M M
 3361 CAGGGAAGTC CTCTACCGAG AGTTCGATGA GATGGAAGAG TGCTCTCAGC ACTTACCGTA CATCGAGCAA GGGATGATGC
 GTCCCTTCAG GAGATGGCTC TCAAGCTACT CTACCTTCTC ACGAGAGTCG TGAATGGCAT GTAGCTCGTT CCTACTACG

+2 L A E Q F K Q K A L G L L Q T A S R Q A E V I A P A V
 3441 TCGCCGAGCA GTTCAAGCAG AAGGCCCTCG GCCTCCTGCA GACCGCGTCC CGTCAGGCAG AGGTTATCGC CCCTGCTGTC
 AGCGGCTCGT CAAGTTCGTC TTCCGGGAGC CGGAGGACGT CTGGCGCAGG GCAGTCCGTC TCCAATAGCG GGGACGACAG

+2 Q T N W Q K L E T F W A K H M W N F I S G I Q Y L A G
 3521 CAGACCAACT GGCAAAAAC TCGAGACCTTC TGGGCGAAGC ATATGTGGAA CTTTCATCAGT GGGATACAAT ACTTGGCGGG
 GTCTGGTTGA CCGTTTTTGA GCTCTGGAAG ACCCGCTTCG TATACACCTT GAAGTAGTCA CCCTATGTTA TGAACCGCCC

+2 L S T L P G N P A I A S L M A F T A A V T S P L T T
 3601 CTTGTCAACG CTGCTGGTA ACCCGCCAT TGCTTCATTG ATGGCTTTTA CAGCTGCTGT CACCAGCCCA CTAACCTA
 GAACAGTTGC GACGACCAT TGGGGCGGTA ACGAAGTAAC TACCGAAAAT GTCGACGACA GTGGTGGGT GATTGGTGTAT

+2 S Q T L L F N I L G G W V A A Q L A A P G A A T A F V
 3681 GCCAAACCTT CCTCTTCAAC ATATTGGGGG GGTGGGTGGC TGCCAGCTC GCCGCCCCG GTGCCGCTAC TGCCTTTGTG
 CGGTTTGGGA GGAGAAGTTG TATAACCCCC CCACCCACCG ACGGGTCGAG CGGCGGGGGC CACGGCGATG ACGGAAACAC

FIGURE 3 - Page 4

+2 G A G L A G A A I G S V G L G K V L I D I L A G Y G A
 3761 GGGCTGGCT TAGCTGGCGC CGCCATCGGC AGTGTGGAC TGGGAAGGT CCTCATAGAC ATCCTTGACG GGTATGGCGC
 CCGCGACCGA ATCGACCGCG GCGGTAGCCG TCACAACTG ACCCCTTCCA GGAGTATCTG TAGGAACGTC CCATACCGCG

+2 G V A G A L V A F K I M S G E V P S T E D L V N L L
 3841 GGGCGTGGCG GGAGCTCTTG TGGCATTCAA GATCATGAGC GGTGAGGTCC CCTCCACGGA GGACCTGGTC AATCTACTGC
 CCCGCACCGC CCTCGAGAAC ACCGTAAGTT CTAGTACTCG CCACTCCAGG GGAGGTGCCT CCTGGACCAG TTAGATGACG

+2 P A I L S P G A L V V G V V C A A I L R R H V G P G E
 3921 CCGCCATCCT CTCGCCCGGA GCCCTCGTAG TCGGCGTGGT CTGTGCAGCA ATACTGCGCC GGCACGTTGG CCCGGGCGAG
 GGCGGTAGGA GAGCGGGCCT CGGGAGCATC AGCCGCACCA GACACGTCGT TATGACGCGG CCGTGCAACC GGGCCCCGCTC

+2 G A V Q . W M N R L I A F A S R G N H V S P T H Y V P E
 4001 GGGCAGTGC AGTGGATGAA CCGGCTGATA GCCTTCGCCT CCCGGGGGAA CCATGTTTCC CCCACGCACT ACGTGCCGGA
 CCCCGTCACG TCACCTACTT GGCCGACTAT CGGAAGCGGA GGGCCCCCTT GGTACAAAGG GGGTGCCTGA TGCACGGCCT

+2 S D A A A R V T A I L S S L T V T Q L L R R L H Q W
 4081 GAGCGATGCA GGTGCCCCGCG TCACTGCCAT ACTCAGCAGC CTCAGTGTAA CCCAGCTCCT GAGGCGACTG CACCACTGGA
 CTCGCTACGT CGACGGGCGC AGTGACGGTA TGAGTCGTCG GAGTGACATT GGGTCGAGGA CTCCGCTGAC GTGGTCACCT

+2 I S S E C T T P C S G S W L R D I W D W I C E V L S D
 4161 TAAGTCGGA GTGTACCACT CCATGCTCCG GTTCCTGGCT AAGGGACATC TGGGACTGGA TATGCGAGGT GTTGAGCGAC
 ATTCGAGCCT CACATGGTGA GGTACGAGGC CAAGGACCGA TTCCCTGTAG ACCCTGACCT ATACGCTCCA CAACTCGCTG

+2 F K T W L K A K L M P Q L P G I P F V S C Q R G Y K G
 BamHI
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 4241 TTTAAGACCT GGCTAAAAGC TAAGCTCATG CCACAGCTGC CTGGGATCCC CTTTGTGTCC TGCCAGCGCG GGTATAAGGG  
 AAATTCTGGA CCGATTTTCG ATTCGAGTAC GGTGTCGACG GACCCTAGGG GAAACACAGG ACGGTGCGCG CCATATTCCC

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+2 V W R G D G I M H T R C H C G A E I T G H V K N G T  
 4321 GGTCTGGCGA GGGGACGGCA TCATGCACAC TCGCTGCCAC TGTGGAGCTG AGTCACTGG ACATGTCAAA AACGGGACGA  
 CCAGACCGCT CCCCTGCCGT AGTACGTGTG AGCGACGGTG ACACCTCGAC TCTAGTGACC TGTACAGTTT TTGCCCTGCT

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+2 M R I V G P R T C R N M W S G T F P I N A Y T T G P C  
 4401 TGAGGATCGT CCGTCCTAGG ACCTGCAGGA ACATGTGGAG TGGGACCTTC CCCATTAATG CCTACACCAC GGGCCCCGTGT  
 ACTCCTAGCA GCCAGGATCC TGGACGTCCT TGTACACCTC ACCCTGGAAG GGGTAATTAC GGATGTGGTG CCCGGGGACA

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+2 T P L P A P N Y T F A L W R V S A E E Y V E I R Q V G  
 4481 ACCCCCCTTC CTGCGCCGAA CTACACGTTT GCGCTATGGA GGGTGTCTGC AGAGGAATAC GTGGAGATAA GGCAGGTGGG  
 TGGGGGGAAG GACGCGGCTT GATGTGCAAG CGCGATACCT CCCACAGACG TCTCCTTATG CACCTCTATT CCGTCCACCC

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+2 D F H Y V T G M T T D N L K C P C Q V P S P E F F T  
 4561 GGAATTCCAC TACGTGACGG GTATGACTAC TGACAATCTT AAATGCCCCG GCCAGGTCCC ATCGCCCGAA TTTTTCACAG  
 CCTGAAGGTG ATGCACTGCC CATACTGATG ACTGTTAGAA TTTACGGGCA CCGTCCAGGG TAGCGGGCTT AAAAAGTGTC

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+2 E L D G V R L H R F A P P C K P L L R E E V S F R V G  
 4641 AATTGGACGG GGTGCGCCTA CATAGGTTTG CGCCCCCTG CAAGCCCTTG CTGCGGGAGG AGGTATCATT CAGAGTAGGA  
 TTAACCTGCC CCACGCGGAT GTATCCAAAC GCGGGGGGAC GTTCGGGAAC GACGCCCTCC TCCATAGTAA GTCTCATCCT

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+2 L H E Y P V G S Q L P C E P E P D V A V L T S M L T D  
 4721 CTCCACGAAT ACCCGGTAGG GTCGCAATTA CCTTGCGAGC CCGAACCGGA CGTGGCCGTG TTGACGTCCA TGCTCACTGA  
 GAGGTGCTTA TGGGCCATCC CAGCGTTAAT GGAACGCTCG GGCTTGGCCT GCACCGGCAC AACTGCAGGT ACGAGTGACT

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+2 P S H I T A E A A G R R L A R G S P P S V A S S S A  
 4801 TCCCTCCCAT ATAACAGCAG AGGCGGCGCG GCGAAGGTTG GCGAGGGGAT CACCCCCCTC TGTGGCCAGC TCCTCGGCTA  
 AGGGAGGGTA TATTGTCGTC TCCGCCGCGC CGCTTCCAAC CGTCCCCTA GTGGGGGGAG ACACCGGTG AGGAGCCGAT

	+2	S Q L S A P S L K A T C T A N H D S P D A E L I E A N
4881	GCCAGCTATC CGCTCCATCT CTCAAGGCAA CTTGCACCGC TAACCATGAC TCCCCTGATG CTGAGCTCAT AGAGGCCAAC CGGTGATAG GCGAGGTAGA GAGTTCGGT GAACGTGGCG ATTGTACTG AGGGGACTAC GACTCGAGTA TCTCCGGTTG	
	+2	L L W R Q E M G G N I T R V E S E N K V V I L D S F D
4961	CTCCTATGGA GGCAGGAGAT GGGCGGCAAC ATCACCAGGG TTGAGTCAGA AAACAAAGTG GTGATTCTGG ACTCCTTCGA GAGGATACTT CCGTCTCTA CCCGCCGTTG TAGTGGTCCC AACCTAGTCT TTTGTTTCAC CACTAAGACC TGAGGAAGCT	
	+2	P L V A E E D E R E I S V P A E I L R K S R R F A Q
5041	TCCGCTTGTT GCGGAGGAGG ACGAGCGGGA GATCTCCGTA CCCGCAGAAA TCCTGCGGAA GTCTCGGAGA TTCGCCCCAG AGGCGAACAC CGCCTCTCTC TGCTCGCCCT CTAGAGGCAT GGGCGTCTTT AGGACGCCTT CAGAGCCTCT AAGCGGGTCC	
	+2	A L P V W A R P D Y N P P L V E T W K K P D Y E P P V
5121	CCCTGCCCCG TTGGGCGCGG CCGGACTATA ACCCCCCGCT AGTGGAGACG TGGAAAAAGC CCGACTACGA ACCACCTGTG GGGACGGGCA AACC CGCGCC GGCTGATAT TGGGGGGCGA TCACCTCTGC ACCTTTTTTC GGCTGATGCT TGGTGGACAC	
	+2	V H G C P L P P P K S P P V P P P R K K R T V V L T E
5201	GTCCATGGCT GCCCGCTTCC ACCTCCAAAG TCCCCTCTG TGCTCCGCC TCGGAAGAAG CGGACGGTGG TCCTCACTGA CAGGTACCGA CGGGCGAAGG TGGAGGTTTC AGGGGAGGAC ACGGAGGCGG AGCCTTCTTC GCCTGCCACC AGGAGTGACT	
	+2	S T L S T A L A E L A T R S F G S S S T S G I T G D
5281	ATCAACCCTA TCTACTGCCT TGGCCGAGCT CGCCACCAGA AGCTTTGGCA GCTCCTCAAC TTCCGGCATT ACGGGCGACA TAGTTGGGAT AGATGACGGA ACCGGCTCGA GCGGTGGTCT TCGAAACCGT CGAGGAGTTG AAGGCCGTAA TGCCCGCTGT	
	+2	N T T T S S E P A P S G C P P D S D A E S Y S S M P P
5361	ATACGACAAC ATCCTCTGAG CCCGCCCTT CTGGCTGCCC CCCCAGCTCC GACGCTGAGT CCTATTCTCT CATGCCCCCC TATGCTGTTG TAGGAGACTC GGGCGGGGAA GACCGACGGG GGGGCTGAGG CTGCGACTCA GGATAAGGAG GTACGGGGGG	
	+2	L E G E P G D P D L S D G S W S T V S S E A N A E D V
		BamHI ~~~~~
5441	CTGGAGGGGG AGCCTGGGGA TCCGGATCTT AGCGACGGGT CATGGTCAAC GGTCAGTAGT GAGGCCAACG CGGAGGATGT GACCTCCCCC TCGGACCCCT AGGCCTAGAA TCGCTGCCCA GTACCAGTTG CCAGTCATCA CTCCGGTTGC GCCTCTACA	
	+2	V C C S M S Y S W T G A L V T P C A A E E Q K L P I
5521	CGTGTGCTGC TCAATGTCTT ACTCTTGAC AGGCGCACTC GTCACCCCGT GCGCGCGGGA AGAACAGAAA CTGCCCATCA GCACACGACG AGTTACAGAA TGAGAACCTG TCCGCGTGAG CAGTGGGGCA CGCGGCGCCT TCTTGTCTTT GACGGGTAGT	
	+2	N A L S N S L L R H H N L V Y S T T S R S A C Q R Q K
5601	ATGCACTAAG CAACTCGTTG CTACGTCACC ACAATTGGT GTATTCCACC ACCTCACGCA GTGCTTGCCA AAGGCAGAAG TACGTGATTG GTTGAGCAAC GATGCAGTGG TGTTAAACCA CATAAGGTGG TGGAGTGCCT CACGAACGGT TTCCGTCTTC	
	+2	K V T F D R L Q V L D S H Y Q D V L K E V K A A A S K
5681	AAAGTCACAT TTGACAGACT GCAAGTTCG GACAGCCATT ACCAGGACGT ACTCAAGGAG GTTAAAGCAG CGGCGTCAAA TTTCAGTGTA AACTGTCTGA CGTTCAAGAC CTGTCGGTAA TGGTCTCTGA TGAGTTCCCT CAATTCGTC GCCGCAGTTT	
	+2	V K A N L L S V E E A C S L T P P H S A K S K F G Y
5761	AGTGAAGGCT AACTTGCTAT CCGTAGAGGA AGCTTGCAGC CTGACGCCCC CACACTCAGC CAAATCCAAG TTTGTTATG TCACTCCGA TTGAACGATA GGCATCTCT TCGAACGTCG GACTGCGGGG GTGTGAGTCG GTTTAGGTTT AAACCAATAC	
	+2	G A K D V R C H A R K A V T H I N S V W K D L L E D N
5841	GGGCAAAAGA CGTCCGTTGC CATGCCAGAA AGGCCGTAAC CCACATCAAC TCCGTGTGGA AAGACCTTCT GGAAGACAAT CCCGTTTTCT GCAGGCAACG GTACGGTCTT TCCGGCATTG GGTGTAGTTG AGGCACACCT TTCTGGAAGA CTTTCTGTTA	
	+2	V T P I D T T I M A K N E V F C V Q P E K G G R K P A
5921	GTAACACCAA TAGACACTAC CATCATGGCT AAGAACGAGG TTTTCTGCGT TCAGCCTGAG AAGGGGGGTC GTAAGCCAGC CATTGTGGTT ATCTGTGATG GTAGTACCGA TTCTTGCTCC AAAAGACGCA AGTCGGACTC TTCCCCCAG CATTGCGTCG	

**FIGURE 3 - Page 6**

	R	L	I	V	F	D	L	G	V	R	V	C	E	K	M	A	L	Y	D	V	V	T	K	L	P		
6001	TCGTCTCATC	GTGTTCCCCG	ATCTGGGCGT	GCGCGTGTGC	GAAAAGATGG	CTTTGTACGA	CGTGGTTACA	AAGCTCCCCT	AGCAGAGTAG	CACAAGGGGC	TAGACCCGCA	CGCGCACACG	CTTTTCTACC	GAAACATGCT	GCACCAATGT	TTCGAGGGGA											
+2	L	A	V	M	G	S	S	Y	G	F	Q	Y	S	P	G	Q	R	V	E	F	L	V	Q	A	W	K	S
																			EcoRI								
6081	TGGCCGTGAT	GGGAAGCTCC	TACGGATTCC	AATACTCACC	AGGACAGCGG	GTTGAATTCC	TCGTGCAAGC	GTGGAAGTCC	ACCGGCACTA	CCCTTCGAGG	ATGCCTAAGG	TTATGAGTGG	TCCTGTGCGC	CAACTTAAGG	AGCACGTTTC	CACCTTCAGG											
+2	K	K	T	P	M	G	F	S	Y	D	T	R	C	F	D	S	T	V	T	E	S	D	I	R	T	E	E
6161	AAGAAAACCC	CAATGGGGTT	CTCGTATGAT	ACCGCTGTCT	TTGACTCCAC	AGTCACTGAG	AGCGACATCC	GTACGGAGGA	TTCTTTTGGG	GTTACCCCAA	GAGCATACTA	TGGGCGACGA	AACTGAGGTG	TCAGTGACTC	TCGCTGTAGG	CATGCTCTCT											
+2	A	I	Y	Q	C	C	D	L	D	P	Q	A	R	V	A	I	K	S	L	T	E	R	L	Y	V	G	
6241	GGCAATCTAC	CAATGTTGTG	ACCTCGACCC	CCAAGCCCGC	GTGGCCATCA	AGTCCCTCAC	CGAGAGGCTT	TATGTTGGGG	CCGTTAGATG	GTTACAACAC	TGGAGCTGGG	GGTTCGGGCG	CACCGGTAGT	TCAGGGAGTG	GCTCTCCGAA	ATACAACCCC											
+2	G	P	L	T	N	S	R	G	E	N	C	G	Y	R	R	C	R	A	S	G	V	L	T	T	S	C	G
6321	GCCCTCTTAC	CAATTCAAGG	GGGGAGAACT	GCGGCTATCG	CAGGTGCCGC	GCGAGCGGCG	TACTGACAAC	TAGCTGTGGT	CGGGAGAAATG	GTTAAGTTCC	CCCCTCTTGA	CGCCGATAGC	GTCCACGGCG	CGCTCGCCGC	ATGACTGTTG	ATCGACACCA											
+2	N	T	L	T	C	Y	I	K	A	R	A	A	C	R	A	A	G	L	Q	D	C	T	M	L	V	C	G
6401	AACACCCTCA	CTTGCTACAT	CAAGGCCCGG	GCAGCCTGTC	GAGCCGCAGG	GCTCCAGGAC	TGCACCATGC	TCGTGTGTGG	TTGTGGGAGT	GAACGATGTA	GTTCCGGGCG	CGTCGGACAG	CTCGGCGTCC	CGAGGTCTCTG	ACGTGGTACG	AGCACACACC											
+2	D	D	L	V	V	I	C	E	S	A	G	V	Q	E	D	A	A	S	L	R	A	F	T	E	A	M	
6481	CGACGACTTA	GTCGTTATCT	GTGAAAGCGC	GGGGGTCCAG	GAGGACGCGG	CGAGCCTGAG	AGCCTTCACG	GAGGCTATGA	GCTGCTGAAT	CAGCAATAGA	CACTTTCGCG	CCCCCAGGTC	CTCCTGCGCC	GCTCGGACTC	TCGGAAGTGC	CTCCGATACT											
+2	T	R	Y	S	A	P	P	G	D	P	P	Q	P	E	Y	D	L	E	L	I	T	S	C	S	S	N	V
6561	CCAGGTACTC	CGCCCCCCTT	GGGGACCCCC	CACAACCAGA	ATACGACTTG	GAGCTCATAA	CATCATGCTC	CTCCAACGTG	GGTCCATGAG	GCGGGGGGGA	CCCCTGGGGG	GTGTTGGTCT	TATGCTGAAC	CTCGAGTATT	GTAGTACGAG	GAGGTTGCAC											
+2	S	V	A	H	D	G	A	G	K	R	V	Y	Y	L	T	R	D	P	T	T	P	L	A	R	A	A	W
6641	TCAGTCGCCC	ACGACGGCGC	TGGAAGAGAGG	GTCTACTACC	TCACCCGTGA	CCCTACAACC	CCCTCGCGA	GAGCTGCGTG	AGTCAGCGGG	TGCTGCCGCG	ACCTTTCTCC	CAGATGATGG	AGTGGGCACT	GGGATGTTGG	GGGGAGCGCT	CTCGACGCAC											
+2	E	T	A	R	H	T	P	V	N	S	W	L	G	N	I	I	M	F	A	P	T	L	W	A	R	M	
6721	GGAGACAGCA	AGACACACTC	CAGTCAATTC	CTGGCTAGGC	AACATAATCA	TGTTTGCCCC	CACACTGTGG	GCGAGGATGA	CCTCTGTCGT	TCTGTGTGAG	GTCAGTTAAG	GACCGATCCG	TTGTATTAGT	ACAAACGGGG	GTGTGACACC	CGCTCTACTT											
+2	I	L	M	T	H	F	F	S	V	L	I	A	R	D	Q	L	E	Q	A	L	D	C	E	I	Y	G	A
6801	TACTGATGAC	CCATTTCTTT	AGCGTCCTTA	TAGCCAGGGA	CCAGCTTGAA	CAGGCCCTCG	ATTGCGAGAT	CTACGGGGCC	ATGACTACTG	GGTAAAGAAA	TCGCAGGAAT	ATCGGTCCCT	GGTCAACTT	GTCCGGGAGC	TAACGCTCTA	GATGCCCGGG											



**FIGURE 3 - Page 7**

+2	R T K L	K L T	P I A	A A G Q	L D L	S G W	F T A G	G Y S G
7121	AGAACAAAGC	TCAAACCTCAC	TCCAATAGCG	GCCGCTGGCC	AGCTGGACTT	GTCCGGCTGG	TTCACGGCTG	GCTACAGCGG
	TCTTGTTTCG	AGTTTTGAGT	AGGTTATCGC	CGGCACCGG	TCGACCTGAA	CAGGCCGACC	AAGTGCCGAC	CGATGTCGCC
+2	G D I	Y H S V	S H A	R P R	W I W F	C L L	L L A	A G V
7201	GGGAGACATT	TATCACAGCG	TGTCTCATGC	CCGGCCCCGC	TGGATCTGGT	TTTGCTACT	CCTGCTTGCT	GCAGGGGTAG
	CCCTCTGTAA	ATAGTGTCCG	ACAGATGTACG	GGCCGGGGCG	ACCTAGACCA	AAACGGATGA	GGACGAACGA	CGTCCCCATC
+2	G I Y L	L P N	R					
7281	GCATCTACCT	CCTCCCCAAC	CGATGAAGGT	TGGGGTAAAC	ACTCCGGCCT	AAAAAAAAA	AAAAATCTAG	AAAGGCGCGC
	CGTAGATGGA	GGAGGGGTTG	GCTACTTCCA	ACCCCATTTG	TGAGGCCGGA	TTTTTTTTT	TTTTTAGATC	TTTCCGCGCG
		BamHI ~~~~~	MluI ~~~~~					
7361	CAAGATATCA	AGGATCCACT	ACGCGTTAGA	GCTCGTGAT	CAGCCTCGAC	TGTGCCTTCT	AGTTGCCAGC	CATCTGTTGT
	GTCTATAGT	TCCTAGGTGA	TGCGCAATCT	CGAGCGACTA	GTCCGGAGCTG	ACACGGAAGA	TCAACGGTCG	GTAGACAACA
7441	TTGCCCTCC	CCCCTGCCTT	CCTTGACCCT	GGAAGGTGCC	ACTCCCACTG	TCCTTTCCTA	ATAAAATGAG	GAAATTGCAT
	AACGGGGAGG	GGGCACGGAA	GGAAGTGGGA	CCTTCCACGG	TGAGGGTGAC	AGGAAAGGAT	TATTTTACTC	CTTTAACGTA
7521	CGCATTGTCT	GAGTAGGTGT	CATTCTATTC	TGGGGGGTGG	GGTGGGGCAG	GACAGCAAGG	GGGAGGATTG	GGAAGACAAT
	GCGTAACAGA	CTCATCCACA	GTAAGATAAG	ACCCCCCACC	CCACCCCGTC	CTGTCGTTCC	CCCTCCTAAC	CCTTCTGTTA
7601	AGCAGGCATG	CTGGGGAGCT	CTTCCGCTTC	CTCGCTCACT	GACTCGCTGC	GCTCGGTCGT	TCGGCTGCGG	CGAGCGGTAT
	TCGTCCGTAC	GACCCCTCGA	GAAGGCGAAG	GAGCGAGTGA	CTGAGCGACG	CGAGCCAGCA	AGCCGACGCC	GCTCGCCATA
7681	CAGCTCACTC	AAAGGCGGTA	ATACGGTTAT	CCACAGAATC	AGGGGATAAC	GCAGGAAAGA	ACATGTGAGC	AAAAGGCCAG
	GTCGAGTGAG	TTTCCGCCAT	TATGCCAATA	GGTGTCTTAG	TCCCTATTG	CGTCCTTTCT	TGTACACTCG	TTTTCCGGTC
7761	CAAAAGGCCA	GGAACCGTAA	AAAGGCCGCG	TTGCTGGCGT	TTTTCCATAG	GCTCCGCCCC	CCTGACGAGC	ATCACAAAAA
	GTTTTCCGGT	CCTTGGCATT	TTTCCGGCGC	AACGACCGCA	AAAAGGTATC	CGAGGCGGGG	GGACTGCTCG	TAGTGTTTTT
7841	TCGACGCTCA	AGTCAGAGGT	GGCGAAACCC	GACAGGACTA	TAAAGATACC	AGGCGTTTCC	CCCTGGAAGC	TCCCTCGTGC
	AGTGCGGAGT	TCAGTCTCCA	CCGCTTTGGG	CTGTCCGTAT	ATTTCTATGG	TCCGCAAAGG	GGGACCTTCG	AGGGAGCACG
7921	GCTCTCCTGT	TCCGACCCTG	CCGCTTACCG	GATACCTGTC	CGCCTTTCTC	CCTTCGGGAA	GCGTGGCGCT	TTCTCAATGC
	CGAGAGGACA	AGGCTGGGAC	GGCGAATGGC	CTATGGACAG	GCGGAAAGAG	GGAAGCCCTT	CGCACC CGCA	AAGAGTTACG
8001	TCACGCTGTA	GGTATCTCAG	TTCGGTGTAG	GTCGTTTCGCT	CCAAGCTGGG	CTGTGTGCAC	GAACCCCCCG	TTCAGCCCGA
	AGTGCGACAT	CCATAGAGTC	AAGCCACATC	CAGCAAGCGA	GGTTCGACCC	GACACACGTG	CTTGGGGGGC	AAGTCGGGCT
8081	CCGCTGCGCC	TTATCCGGTA	ACTATCGTCT	TGAGTCCAAC	CCGGTAAGAC	ACGACTTATC	GCCACTGGCA	GCAGCCACTG
	GGCGACGCGG	AATAGGCCAT	TGATAGCAGA	ACTCAGGTTG	GGCCATTCTG	TGCTGAATAG	CGGTGACCGT	CGTCGGTGAC
8161	GTAACAGGAT	TAGCAGAGCG	AGGTATGTAG	GCGGTGCTAC	AGAGTTCTTG	AAGTGGTGGC	CTAACTACGG	CTACACTAGA
	CATTGTCCTA	ATCGTCTCGC	TCCATACATC	CGCCACGATG	TCTCAAGAAC	TTCACCACCG	GATTGATGCC	GATGTGATCT
8241	AGGACAGTAT	TTGGTATCTG	CGTCTGCTG	AAGCCAGTTA	CCTTCGGAAA	AAGAGTTGGT	AGCTCTTGAT	CCGGCAAACA
	TCCTGTCATA	AACCATAGAC	GCGAGACGAC	TTCGGTCAAT	GGAAGCCTTT	TTCTCAACCA	TCGAGAACTA	GGCCGTTTGT
8321	AACCACCGCT	GGTAGCGGTG	GTTTTTTTGT	TTGCAAGCAG	CAGATTACGC	GCAGAAAAAA	AGGATCTCAA	GAAGATCCTT
	TTGGTGGCGA	CCATCGCCAC	CAAAAAAACA	AACGTTTCGTC	GTCTAATGCG	CGTCTTTTTT	TCCTAGAGTT	CTTCTAGGAA
8401	TGATCTTTTC	TACGGGGTCT	GACGCTCAGT	GGAACGAAAA	CTCACGTTAA	GGGATTTTGG	TCATGAGATT	ATCAAAAAGG
	ACTAGAAAAAG	ATGCCCCAGA	CTGCGAGTCA	CCTTGCTTTT	GAGTGCAATT	CCCTAAAACC	AGTACTCTAA	TAGTTTTTCC

## FIGURE 3 - Page 8

8481 ATCTTCACCT AGATCCTTTT AAATTAAAAA TGAAGTTTTA AATCAATCTA AAGTATATAT GAGTAAACTT GGTCTGACAG  
TAGAAGTGGA TCTAGGAAAA TTTAATTTTT ACTTCAAAAT TTAGTTAGAT TTCATATATA CTCATTTGAA CCAGACTGTC

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8561 TTACCAATGC TTAATCAGTG AGGCACCTAT CTCAGCGATC TGTCTATTTT GTTCATCCAT AGTTGCCTGA CTCCTCGTCG  
AATGGTTACG AATTAGTCAC TCCGTGGATA GAGTCGCTAG ACAGATAAAG CAAGTAGGTA TCAACGGACT GAGGGGCAGC

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8641 TGTAGATAAC TACGATACGG GAGGGCTTAC CATCTGGCCC CAGTGCTGCA ATGATACCGC GAGACCCACG CTCACCGGCT  
ACATCTATTG ATGCTATGCC CTCCGAATG GTAGACCGGG GTCACGACGT TACTATGGCG CTCTGGGTGC GAGTGGCCGA

---

8721 CCAGATTTAT CAGCAATAAA CCAGCCAGCC GGAAGGGCCG AGCGCAGAAG TGGTCCTGCA ACTTTATCCG CCTCCATCCA  
GGTCTAAATA GTCGTTATTT GGTCGGTCCG CCTTCCCGGC TCGCGTCTTC ACCAGGACGT TGAAATAGGC GGAGGTAGGT

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8801 GTCTATTAAT TGTGCGGGG AAGCTAGAGT AAGTAGTTCG CCAGTTAATA GTTTGCGCAA CGTTGTTGCC ATTGCTACAG  
CAGATAATTA ACAACGGCCC TTCGATCTCA TTCATCAAGC GGTCAATTAT CAAACGCGTT GCAACAACGG TAACGATGTC

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8881 GCATCGTGGT GTCACGCTCG TCGTTTGGA TGGCTTCATT CAGCTCCGGT TCCCAACGAT CAAGGCGAGT TACATGATCC  
CGTAGCACCA CAGTGCGAGC AGCAAACCAT ACCGAAGTAA GTCGAGGCCA AGGGTTGCTA GTTCCGCTCA ATGTACTAGG

---

8961 CCCATGTTGT GCAAAAAAGC GGTTAGCTCC TTCGGTCTC CGATCGTTGT CAGAAGTAAG TTGGCCGCAG TGTATCACT  
GGGTACAACA CGTTTTTTCG CCAATCGAGG AAGCCAGGAG GCTAGCAACA GTCTTCATTC AACC GGCGTC ACAATAGTGA

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9041 CATGGTTATG GCAGCACTGC ATAATTCTCT TACTGTCATG CCATCCGTAA GATGCTTTTC TGTGACTGGT GAGTACTCAA  
GTACCAATAC CGTCGTGACG TATTAAGAGA ATGACAGTAC GGTAGGCATT CTACGAAAAG AACTGACCA CTCATGAGTT

---

9121 CCAAGTCATT CTGAGAATAG TGTATGCGGC GACCGAGTTG CTCTTGCCCG GCGTCAATAC GGGATAATAC CGCGCCACAT  
GGTTCAGTAA GACTCTTATC ACATACGCCG CTGGCTCAAC GAGAACGGGC CGCAGTTATG CCCTATTATG GCGCGGTGTA

---

9201 AGCAGAACTT TAAAGTGCT CATCATTGGA AAACGTTCTT CGGGGCGAAA ACTCTCAAGG ATCTTACCGC TGTGAGATC  
TCGTCTTGAA ATTTTCACGA GTAGTAACCT TTTGCAAGAA GCCCGCTTT TGAGAGTTCC TAGAATGGCG ACAACTCTAG

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9281 CAGTTCGATG TAACCCACTC GTGCACCCAA CTGATCTTCA GCATCTTTTA CTTTCACCAG CGTTTCTGGG TGAGCAAAAA  
GTCAAGCTAC ATTGGGTGAG CACGTGGGTT GACTAGAAGT CGTAGAAAAT GAAAGTGGTC GCAAAGACCC ACTCGTTTTT

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9361 CAGGAAGGCA AAATGCCGCA AAAAAGGGAA TAAGGGCGAC ACGGAAATGT TGAATACTCA TACTCTTCTT TTTTCAATAT  
GTCCTTCCGT TTTACGGCGT TTTTCCCTT ATTCCCGCTG TGCCTTTACA ACTTATGAGT ATGAGAAGGA AAAAGTTATA

---

9441 TATTGAAGCA TTTATCAGGG TTATTGTCTC ATGAGCGGAT ACATATTTGA ATGTATTTAG AAAAATAAAC AAATAGGGGT  
ATAACTTCGT AAATAGTCCC AATAACAGAG TACTCGCCTA TGTATAAACT TACATAAATC TTTTATTG TTTATCCCA

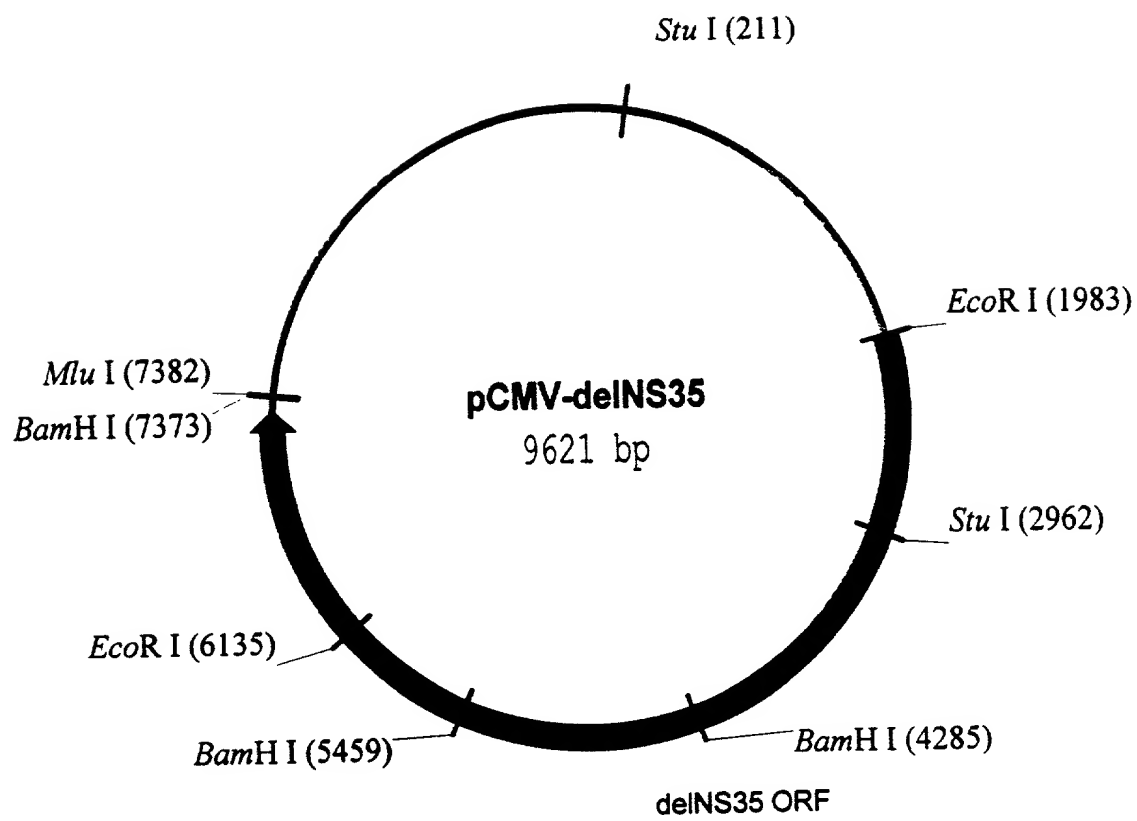
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9521 TCCGCGCACA TTTCCCCGAA AAGTGCCACC TGACGTCTAA GAAACCATTA TTATCATGAC ATTAACCTAT AAAAATAGGC  
AGGCGCGTGT AAAGGGGCTT TTCACGGTGG ACTGCAGATT CTTTGGTAAT AATAGTACTG TAATTGGATA TTTTATCCG

---

9601 GTATCAGGAG GCCCTTTCGT C  
CATAGTGCTC CGGAAAGCA G

FIGURE 4



## FIGURE 5 - Page 1

1 TCGCGCGTTT CGGTGATGAC GGTGAAAACC TCTGACACAT GCAGCTCCCG GAGACGGTCA CAGCTTGTCT GTAAGCGGAT  
AGCGCGCAAA GCCACTACTG CCACCTTTTG AGACTGTGTA CGTCGAGGGC CTCTGCCAGT GTCGAACAGA CATTGCGCTA

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81 GCCGGGAGCA GACAAGCCCG TCAGGGCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCTGG CTTAACTATG CGGCATCAGA  
CGGCCCTCGT CTGTTGCGGC AGTCCCGCGC AGTCGCCCAC AACCGCCCAC AGCCCCGACC GAATTGATAC GCCGTAGTCT

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161 GCAGATTGTA CTGAGAGTGC ACCATATGAA GCTTTTGTGA AAAGCCTAGG CCTCCAAAAA AGCCTCCTCA CTACTTCTGG
CGTCTAACAT GACTCTCAGC TGGTATACTT CGAAAAACGT TTTCGGATCC GGAGGTTTTT TCGGAGGAGT GATGAAGACC

241 AATAGCTCAG AGGCCGAGGC GGCCTCGGCC TCTGCATAAA TAAAAAAAT TAGTCAGCCA TGGGGCGGAG AATGGGCGGA
TTATCGAGTC TCCGGTCCG CCGGAGCCGG AGACGTATTT ATTTTTTTTA ATCAGTCGGT ACCCGCGCTC TTACCCGCTC

321 ACTGGGCGGG GAGGGAATTA TTGGCTATTG GCCATTGCAT ACGTTGTATC TATATCATAA TATGTACATT TATATTGGCT
TGACCCGCCC CTCCCTTAAT AACCGATAAC CGGTAACGTA TGCAACATAG ATATAGTATT ATACATGTAA ATATAACCGA

401 CATGTCCAAT ATGACCGCCA TGTGACATT GATTATTGAC TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT
GTACAGGTTA TACTGGCGGT ACAACTGTAA CTAATAACTG ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA

481 AGCCCATATA TGGAGTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCAACGACC CCCGCCATT
TCGGGTATAT ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC GGGTTGCTGG GGGCGGGTAA

561 GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTACGGT
CTGCAGTTAT TACTGCATAC AAGGGTATCA TTGCGGTTAT CCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

641 AAAGTGGCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTCCGCCC CCTATTGACG TCAATGACGG TAAATGGCCC
TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCAGGCGGG GGATAACTGC AGTTACTGCC ATTTACCGGG

721 GCCTGGCATT ATGCCCAGTA CATGACCTTA CGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA TCGCTATTAC
CGGACCGTAA TACGGGTCAT GTACTGGAAT GCCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT AGCGATAATG

801 CATGGTGATG CGGTTTTGGC AGTACACCAA TGGGCGTGGA TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA
GTACCACTAC GCCAAAACCG TCATGTGGTT ACCCGCACCT ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT

881 TTGACGTCAA TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA ATAACCCCGC CCCGTTGACG
AACTGCAGTT ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT TATTGGGGCG GGGCAACTGC

961 CAAATGGGCG GTAGGCGTGT ACGGTGGGAG GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG
GTTTACCCGC CATCCGCACA TGCCACCTC CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

1041 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC TCCGCGGCCG GGAACGGTGC ATTGGAACGC
GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTGCG AGGCGCCGGC CCTTGCCACG TAACCTTGCG

1121 GGATTCCCCG TGCCAAGAGT GACGTAAGTA CCGCCTATAG ACTCTATAGG CACACCCCTT TGGCTCTTAT GCATGCTATA
CCTAAGGGGC ACGGTTCTCA CTGCATTCAT GGCGGATATC TGAGATATCC GTGTGGGGAA ACCGAGAATA CGTACGATAT

1201 CTGTTTTTGG CTTGGGGCCT ATACACCCCC GTCCTTTATG CTATAGGTGA TGGTATAGCT TAGCCTATAG GTGTGGGTTA
GACAAAACCG GAACCCCGGA TATGTGGGGG CGAGGAATAC GATATCCACT ACCATATCGA ATCGGATATC CACACCCAAT

1281 TTGACCATT AATGACCTC CCCTATTGGT GACGATACTT TCCATTACTA ATCCATAACA TGGCTCTTTG CCACAACAT
AATGGAAT AACTGGTGAG GGGATAACCA CTGCTATGAA AGGTAATGAT TAGGTATTGT ACCGAGAAAC GGTGTTGATA

1361 CTCTATTGGC TATATGCCAA TACTCTGTCC TTCAGAGACT GACACGGACT CTGTATTTTT ACAGGATGGG GTCCATTTAT
GAGATAACCG ATATACGGTT ATGAGACAGG AAGTCTCTGA CTGTGCCTGA GACATAAAAA TGTCCTACCC CAGGTAAATA

FIGURE 5 - Page 2

1441 TATTTACAAA TTCACATATA CAACAACGCC GTCCCCCGTG CCCGCAGTTT TTATTAAACA TAGCGTGGGA TCTCCGACAT
ATAAATGTTT AAGTGTATAT GTTGTTCGGG CAGGGGGCAC GGGCGTCAAA AATAATTGT ATCGCACCT AGAGGCTGTA

1521 CTCGGGTACG TGTTCCGGAC ATGGGCTCTT CTCCGGTAGC GCGGAGCTT CCACATCCGA GCCCTGGTCC CATCCGTCCA
GAGCCCATGC ACAAGGCCG TACCCGAGAA GAGGCCATCG CCGCCTCGAA GGTGTAGGCT CGGGACCAGG GTAGGCAGGT

1601 GCGGCTCATG GTCGCTCGGC AGCTCCTTGC TCCTAACAGT GGAGGCCAGA CTTAGGCACA GCACAATGCC CACCACCACC
CGCCGAGTAC CAGCGAGCCG TCGAGGAACG AGGATTGTCA CCTCCGGTCT GAATCCGTGT CGTGTTACGG GTGGTGGTGG

1681 AGTGTGCCGC ACAAGGCCGT GGCGGTAGGG TATGTGTCTG AAAATGAGCT CGGAGATTGG GCTCGCACCT GGACGCAGAT
TCACACGGCG TGTTCCGGCA CCGCCATCCC ATACACAGAC TTTTACTCGA GCCTCTAACC CGAGCGTGGG CCTGCGTCTA

1761 GGAAGACTTA AGGCAGCGGC AGAAGAAGAT GCAGGCAGCT GAGTTGTTGT ATTCTGATAA GAGTCAGAGG TAACTCCCGT
CCTTCTGAAT TCCGTCGCCG TCTTCTTCTA CGTCCGTCGA CTCAACAACA TAAGACTATT CTCAGTCTCC ATTGAGGGCA

1841 TGCGGTGCTG TTAACGGTGG AGGGCAGTGT AGTCTGAGCA GTACTCGTTG CTGCCGCGCG CGCCACCAGA CATAATAGCT
ACGCCACGAC AATTGCCACC TCCCGTCACA TCAGACTCGT CATGAGCAAC GACGGCGCGC GCGGTGGTCT GTATTATCGA

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1921 GACAGACTAA CAGACTGTTT CTTTCCATGG GTCTTTTCTG CAGTCACCGT CGTCGACCTA AGAATTCACC ATGGCTGCAT  
CTGTCTGATT GTCTGACAAG GAAAGGTACC CAGAAAAGAC GTCAGTGGCA GCAGCTGGAT TCTTAAGTGG TACCGACGTA

+2 Y A A Q G Y K V L V L N P S V A A T L G F G A Y M S K  
2001 ATGCAGCTCA GGGCTATAAG GTGCTAGTAC TCAACCCCTC TGTTGCTGCA AACTGGGCT TTGGTGCTTA CATGTCCAAG  
TACGTCGAGT CCCGATATTC CACGATCATG AGTTGGGGAG ACAACGACGT TGTGACCCGA AACCACGAAT GTACAGGTTT

+2 A H G I D P N I R T G V R T I T T G S P I T Y S T Y G  
2081 GCTCATGGGA TCGATCCTAA CATCAGGACC GGGGTGAGAA CAATTACCAC TGGCAGCCCC ATCAGTACT CCACCTACGG  
CGAGTACCCT AGCTAGGATT GTAGTCCTGG CCCCCTCTT GTTAATGGTG ACCGTCGGGG TAGTGATGA GGTGGATGCC

+2 K F L A D G G C S G G A Y D I I I C D E C H S T D A  
2161 CAAGTTCCTT GCCGACGGCG GGTGCTCGGG GGGCGCTTAT GACATAATAA TTTGTGACGA GTGCCACTCC ACGGATGCCA  
GTTCAAGGAA CGGCTGCCGC CCACGAGCCC CCCGCAATA CTGTATTATT AAACACTGCT CACGGTGAGG TGCCTACGGT

+2 T S I L G I G T V L D Q A E T A G A R L V V L A T A T  
2241 CATCCATCTT GGGCATTGGC ACTGTCCTTG ACCAAGCAGA GACTGCGGGG GCGAGACTGG TTGTGCTCGC CACCGCCACC  
GTAGGTAGAA CCCGTAACCG TGACAGGAAC TGGTTCGTCT CTGACGCCCC CGCTCTGACC AACACGAGCG GTGGCGGTGG

+2 P P G S V T V P H P N I E E V A L S T T G E I P F Y G  
2321 CCTCCGGGCT CCGTCACTGT GCCCCATCCC AACATCGAGG AGGTTGCTCT GTCCACCACC GGAGAGATCC CTTTTTACGG  
GGAGGCCCGA GGCAGTGACA CGGGGTAGGG TTGTAGCTCC TCCAACGAGA CAGGTGGTGG CCTCTCTAGG GAAAAATGCC

+2 K A I P L E V I K G G R H L I F C H S K K K C D E L  
2401 CAAGGCTATC CCCCTCGAAG TAATCAAGGG GGGGAGACAT CTCATCTTCT GTCATTCAAA GAAGAAGTGC GACGAACCTG  
GTTCCGATAG GGGGAGCTTC ATTAGTTCCC CCCCTCTGTA GAGTAGAAGA CAGTAAGTTT CTCTTCACG CTGCTTGAGC

+2 A A K L V A L G I N A V A Y Y R G L D V S V I P T S G  
2481 CCGCAAAGCT GGTGCGATTG GGCATCAATG CCGTGGCCTA CTACCGCGGT CTTGACGTGT CCGTCATCCC GACCAGCGGG  
GGCGTTTCGA CCAGCGTAAC CCGTAGTTAC GGCACCGGAT GATGGCGCCA GAACTGCACA GGCAGTAGGG CTGGTCGCCG

+2 D V V V V A T D A L M T G Y T G D F D S V I D C N T C  
2561 GATGTTGTCG TCGTGGCAAC CGATGCCCTC ATGACCGGCT ATACCGGCGA CTTGACTCG GTGATAGACT GCAATACGTG  
CTACAACAGC AGCACCGTTG GCTACGGGAG TACTGGCCGA TATGGCCGCT GAAGCTGAGC CACTATCTGA CGTTATGCAC

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**FIGURE 5 - Page 3**

+2    V   T   Q    T   V   D   F    S   L   D    P   T   F    T   I   E   T    I   T   L    P   Q   D    A   V   S  
 2641   TGTCACCCAG   ACAGTCGATT   TCAGCCTTGA   CCCTACCTTC   ACCATTGAGA   CAATCAGCT   CCCCCAAGAT   GCTGTCTCCC  
       ACAGTGGGTC   TGTCAGCTAA   AGTCGGAACT   GGGATGGAAG   TGGTAACTCT   GTTAGTGCGA   GGGGGTTCTA   CGACAGAGGG

+2 R T Q R R G R T G R G K P G I Y R F V A P G E R P S G  
 2721 GCACTCAACG TCGGGGCAGG ACTGGCAGGG GGAAGCCAGG CATCTACAGA TTTGTGGCAC CGGGGGAGCG CCCCTCCGGC  
 CGTGAGTTGC AGCCCCGTCC TGACCGTCCC CCTTCGGTCC GTAGATGTCT AAACACCGTG GCCCCCTCGC GGGGAGGCCG

+2 M F D S S V L C E C Y D A G C A W Y E L T P A E T T V  
 2801 ATGTTCTGACT CGTCCGTCCT CTGTGAGTGC TATGACGCAG GCTGTGCTTG GTATGAGCTC ACGCCCGCCG AGACTACAGT  
 TACAAGCTGA GCAGGCAGGA GACACTCAGC ATACTGCGTC CGACACGAAC CATACTCGAG TGCGGGCGGC TCTGATGTCA

[illegible]

+2 G L T H I D A H F L S Q T K Q S G E N L P Y L V A Y Q  
 StuI  
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 2961 GCCTCACTCA TATAGATGCC CACTTTCTAT CCCAGACAAA GCAGAGTGGG GAGAACCTTC CTTACCTGGT AGCGTACCAA
 CGGAGTGAGT ATATCTACGG GTGAAAGATA GGGTCTGTTT CGTCTCACCC CTCTTGAAG GAATGGACCA TCGCATGGTT

+2 A T V C A R A Q A P P P S W D Q M W K C L I R L K P T
 3041 GCCACCGTGT GCGCTAGGGC TCAAGCCCCT CCCCCATCGT GGGACCAGAT GTGGAAGTGT TTGATTGCC TCAAGCCCAC
 CGGTGGCACA CGCGATCCCG AGTTCGGGGA GGGGGTAGCA CCCTGGTCTA CACCTTCACA AACTAAGCGG AGTTCGGGGT

+2 L H G P T P L L Y R L G A V Q N E I T L T H P V T K
 3121 CCTCCATGGG CCAACACCCC TGCTATACAG ACTGGGCGCT GTTCAGAATG AAATCACCCCT GACGCACCCA GTCACCAAAT
 GGAGGTACCC GGTGTGGGG ACGATATGTC TGACCCGCGA CAAGTCTTAC TTTAGTGGGA CTGCGTGGGT CAGTGGTTTA

+2 Y I M T C M S A D L E V V T S T W V L V G G V L A A L
 3201 ACATCATGAC ATGCATGTCG GCCGACCTGG AGGTCGTAC GAGCACCTGG GTGCTCGTTG GCGGCGTCCT GGCTGCTTTG
 TGTAGTACTG TACGTACAGC CGGCTGGACC TCCAGCAGTG CTCGTGGACC CACGAGCAAC CGCCGCAGGA CCGACGAAAC

+2 A A Y C L S T G C V V I V G R V V L S G K P A I I P D
3281 GCCGCGTATT GCCTGTCAAC AGGCTGCGTG GTCATAGTGG GCAGGGTCTG CTGTGCCGGG AAGCCGGCAA TCATACCTGA
CGGCGCATAA CGGACAGTTG TCCGACGCAC CAGTATCACC CGTCCCAGCA GAACAGGCCC TTCGGCCGTT AGTATGGACT

+2 R E V L Y R E F D E M E E C S Q H L P Y I E Q G M M
 3361 CAGGGAAGTC CTCTACCGAG AGTTGCATGA GATGGAAGAG TGCTCTCAGC ACTTACCGTA CATCGAGCAA GGGATGATGC
 GTCCCTTCAG GAGATGGCTC TCAAGCTACT CTACCTTCTC ACGAGAGTCG TGAATGGCAT GTAGCTCGTT CCCTACTACG

+2 L A E Q F K Q K A L G L L Q T A S R Q A E V I A P A V
 3441 TCGCCGAGCA GTTCAAGCAG AAGGCCCTCG GCCTCCTGCA GACCGCGTCC CGTCAGGCAG AGGTTATCGC CCCTGCTGTC
 AGCGGCTCGT CAAGTTCGTC TTCCGGGAGC CGGAGGACGT CTGGCGCAGG GCAGTCCGTC TCCAATAGCG GGGACGACAG

+2 Q T N W Q K L E T F W A K H M W N F I S G I Q Y L A G
3521 CAGACCAACT GGCAAAACT CGAGACCTTC TGGGCGAAGC ATATGTGGAA CTTTCATCAGT GGGATACAAT ACTTGGCGGG
GTCTGTTGA CCGTTTTTGA GCTCTGGAAG ACCCGCTTCG TATACACCTT GAAGTAGTCA CCCTATGTTA TGAACCGCCC

+2 L S T L P G N P A I A S L M A F T A A V T S P L T T
 3601 CTTGTCAACG CTGCCTGGTA ACCCCGCCAT TGCTTCATTG ATGGCTTTTA CAGCTGCTGT CACCAGCCCA CTAACCACTA
 GAACAGTTGC GACGGACCAT TGGGGCGGTA ACGAAGTAAC TACCGAAAT GTCGACGACA GTGGTCGGGT GATTGGTGAT

3681 +2 S Q T L L F N I L G G W V A A Q L A A P G A A T A F V
GCCAAACCTT CCTCTTCAAC ATATTGGGGG GGTGGGTGGC TGCCAGCTC GCCGCCCCG GTGCCGCTAC TGCTTTGTG
CGGTTTGGGA GGAGAACTTG TATAACCCC CACCCACCG ACGGGTCGAG CGGCGGGGGC CACGGCGATG ACGGAAACAC

FIGURE 5 - Page 4

+2 G A G L A G A A I G S V G L G K V L I D I L A G Y G A
 3761. GGCCTGGCT TAGCTGGCGC CGCCATCGGC AGTGTGGAC TGGGGAAGGT CCTCATAGAC ATCCTTGCAG GGTATGGCGC
 CCCGACCGA ATCGACCGC GCGGTAGCCG TCACAACCTG ACCCCTTCCA GGAGTATCTG TAGGAACGTC CCATACCGC

+2 G V A G A L V A F K I M S G E V P S T E D L V N L L
 3841 GGCCTGGCG GGAGCTCTTG TGGCATTCAA GATCATGAGC GGTGAGGTCC CCTCCACGGA GGACCTGGTC AATCTACTGC
 CCCGACCGC CCTCGAGAAC ACCGTAAGTT CTAGTACTCG CCACTCCAGG GGAGGTGCCT CCTGGACCAG TTAGATGACG

+2 P A I L S P G A L V V G V V C A A I L R R H V G P G E
 3921 CCGCCATCCT CTCGCCCCGA GCCCTCGTAG TCGGCGTGGT CTGTGCAGCA ATACTGCGCC GGCACGTTGG CCCGGGCGAG
 GCGGCTAGGA GAGCGGGCCT CGGGAGCATC AGCCGCACCA GACACGTCGT TATGACGCGG CCGTGCAACC GGGCCCCGCT

+2 G A V Q W M N R L I A F A S R G N H V S P T H Y V P E
 4001 GGGCAGTGC AGTGGATGAA CCGGCTGATA GCCTTCGCCT CCCGGGGGAA CCATGTTTCC CCCACGCACT ACGTGCCGGA
 CCCCCTCAG TCACCTACTT GGCCGACTAT CGGAAGCGGA GGGCCCCCTT GGTACAAAGG GGTGCGTGA TGCACGGCCT

+2 S D A A A R V T A I L S S L T V T Q L L R R L H Q W
 4081 GAGCGATGCA GCTGCCCGC TCACTGCCAT ACTCAGCAGC CTCAGTGTA CCCAGTCTCT GAGGCGACTG CACCACTGGA
 CTCGCTACGT CGACGGGCGC AGTGACGGTA TGAGTCGTCG GAGTGACATT GGTGCGAGGA CTCCGCTGAC GTGGTCACCT

+2 I S S E C T T P C S G S W L R D I W D W I C E V L S D
 4161 TAAGCTCGGA GTGTACCACT CCATGTCCG GTTCCTGGCT AAGGGACATC TGGGACTGGA TATGCGAGGT GTTGAGCGAC
 ATTCGAGCCT CACATGGTGA GGTACGAGGC CAAGGACCGA TTCCCTGTAG ACCCTGACCT ATACGTTCCA CAACTCGTG

+2 F K T W L K A K L M P Q L P G I P F V S C Q R G Y K G
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 4241 TTTAAGACCT GGCTAAAAGC TAAGCTCATG CCACAGCTGC CTGGGATCCC CTTTGTGTCC TGCCAGCGCG GGTATAAGGG  
 AAATTCTGGA CCGATTTTCG ATTCGAGTAC GGTGTCGACG GACCCTAGGG GAAACACAGG ACGGTCGCGC CCATATTCCC

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+2 V W R G D G I M H T R C H C G A E I T G H V K N G T  
 4321 GGTCTGGCGA GGGGACGGCA TCATGCACAC TCGCTGCCAC TGTGGAGCTG AGATCACTGG ACATGTCAAA AACGGGACGA  
 CCAGACCGCT CCCCTGCCGT AGTACGTGTG AGCGACGGTG ACACCTCGAC TCTAGTGACC TGTACAGTTT TTGCCCTGCT

---

+2 M R I V G P R T C R N M W S G T F P I N A Y T T G P C  
 4401 TGAGGATCGT CGGTCCTAGG ACCTGCAGGA ACATGTGGAG TGGGACCTTC CCCATTAATG CCTACACCAC GGGCCCCCTGT  
 ACTCCTAGCA GCCAGGATCC TGGACGTCCT TGTACACCTC ACCCTGGAAG GGGTAATTAC GGATGTGGTG CCCGGGGACA

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+2 T P L P A P N Y T F A L W R V S A E E Y V E I R Q V G  
 4481 ACCCCCCCTC CTGCGCCGAA CTACACGTTT GCGCTATGGA GGGTGTCTGC AGAGGAATAC GTGGAGATAA GGCAGGTGGG  
 TGGGGGGAAG GACGCGGCTT GATGTGCAAG CGCGATACCT CCCACAGACG TCTCCTTATG CACCTCTATT CCGTCCACCC

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+2 D F H Y V T G M T T D N L K C P C Q V P S P E F F T  
 4561 GGACTTCCAC TACGTGACGG GTATGACTAC TGACAATCTT AAATGCCCCG GCCAGGTCCC ATCGCCCGAA TTTTTCACAG  
 CCTGAAGGTG ATGCACTGCC CATACTGATG ACTGTTAGAA TTTACGGGCA CCGTCCAGGG TAGCGGGCTT AAAAAGTGTC

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+2 E L D G V R L H R F A P P C K P L L R E E V S F R V G  
 4641 AATTGGACGG GGTGCGCCTA CATAGTTTG CGCCCCCTG CAAGCCCTTG CTGCGGGAGG AGGTATCATT CAGAGTAGGA  
 TTAACCTGCC CCACGCGGAT GTATCCAAAC GCGGGGGGAC GTTCGGGAAC GACGCCCTCC TCCATAGTAA GTCTCATCTT

---

+2 L H E Y P V G S Q L P C E P E P D V A V L T S M L T D  
 4721 CTCCACGAAT ACCCGGTAGG GTCGCAATTA CCTTGCAGC CCGAACCAGA CGTGGCCGTG TTGACGTCCA TGCTCACTGA  
 GAGGTGCTTA TGGGCCATCC CAGCGTTAAT GGAACGCTCG GGCTTGGCTT GCACCGGCAC AACTGCAGGT ACGAGTACT

---

+2 P S H I T A E A A G R R L A R G S P P S V A S S S A  
 4801 TCCCTCCCAT ATAACAGCAG AGGCGGGCCG GCGAAGGTTG GCGAGGGGAT CACCCCCCTC TGTGGCCAGC TCCTCGGCTA  
 AGGGAGGGTA TATTGTCGTC TCCGCCGGCC CGCTTCCAAC CGCTCCCCTA GTGGGGGGAG ACACCGGTG AGGAGCCGAT

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**FIGURE 5 - Page 5**

4881	S	Q	L	S	A	P	S	L	K	A	T	C	T	A	N	H	D	A	S	P	D	A	E	L	I	E	A	N
	GCCAGCTATC	CGCTCCATCT	CTCAAGGCAA	CTTGCACCGC	TAACCATGAC	TCCCCTGATG	CTGAGCTCAT	AGAGGCCAAC	CGGTCGATAG	GCGAGGTAGA	GAGTTCCGTT	GAACGTGGCG	ATTGGTACTG	AGGGGACTAC	GACTCGAGTA	TCTCCGTTG												
+2	L	L	W	R	Q	E	M	G	G	N	I	T	R	V	E	S	E	N	K	V	V	I	L	D	S	F	D	
4961	CTCCTATGGA	GGCAGGAGAT	GGGCGGCAAC	ATCACCAGGG	TTGAGTCAGA	AAACAAAGTG	GTGATTCTGG	ACTCCTTCGA	GAGGATACCT	CCGTCTCTTA	CCCGCCGTTG	TAGTGGTCCC	AACTCAGTCT	TTTGTTCAC	CACTAAGACC	TGAGGAAGCT												
+2	P	L	V	A	E	E	D	E	R	E	I	S	V	P	A	E	I	L	R	K	S	R	R	F	A	Q		
5041	TCCGCTTGTTG	GCGGAGGAGG	ACGAGCGGGA	GATCTCCGTA	CCCGCAGAAA	TCCTGCGGAA	GTCTCGGAGA	TTGCGCCAGG	AGGCGAACAC	CGCTCTCTCC	TGCTCGCCCT	CTAGAGGCAT	GGGCGTCTTT	AGGACGCCTT	CAGAGCCTCT	AAGCGGGTCC												
+2	A	L	P	V	W	A	R	P	D	Y	N	P	P	L	V	E	T	W	K	K	P	D	Y	E	P	P	V	
5121	CCCTGCCCCG	TTGGGCGCGG	CCGGACTATA	ACCCCCCGCT	AGTGGAGACG	TGGAAAAAGC	CCGACTACGA	ACCACCTGTG	GGGACGGGCA	AACCCGCGCC	GGCCTGATAT	TGGGGGGCGA	TCACCTCTGC	ACCTTTTTCG	GGCTGATGCT	TGGTGGACAC												
+2	V	H	G	C	P	L	P	P	P	K	S	P	P	V	P	P	P	R	K	K	R	T	V	V	L	T	E	
5201	GTCCATGGCT	GCCCGCTTCC	ACCTCCAAAG	TCCCCTCTCTG	TGCCTCCGCC	TCGGAAGAAG	CGGACGGTGG	TCCTCACTGA	CAGGTACCGA	CGGGCGAAGG	TGGAGGTTTC	AGGGGAGGAC	ACGGAGGCGG	AGCCTTCTTC	GCCTGCCACC	AGGAGTGACT												
+2	S	T	L	S	T	A	L	A	E	L	A	T	R	S	F	G	S	S	S	T	S	G	I	T	G	D		
5281	ATCAACCCTA	TCTACTGCCT	TGGCCGAGCT	CGCCACCAGA	AGCTTTGGCA	GCTCCTCAAC	TTCCGGCATT	ACGGGCGACA	TAGTTGGGAT	AGATGACGGA	ACCGGCTCGA	GCGGTGGTCT	TCGAAACCGT	CGAGGAGTTG	AAGGCCGTAA	TGCCCGCTGT												
+2	N	T	T	T	S	S	E	P	A	P	S	G	C	P	P	D	S	D	A	E	S	Y	S	S	M	P	P	
5361	ATACGACAAC	ATCCTCTGAG	CCCGCCCCCT	CTGGCTGCCC	CCCCGACTCC	GACGCTGAGT	CCTATTCTCT	CATGCCCCCC	TATGCTGTTG	TAGGAGACTC	GGGCGGGGAA	GACCGACGGG	GGGGCTGAGG	CTGCGACTCA	GGATAAGGAG	GTACGGGGGG												
+2	L	E	G	E	P	G	D	P	D	L	S	D	G	S	W	S	T	V	S	S	E	A	N	A	E	D	V	
							BamHI																					
5441	CTGGAGGGGG	AGCCTGGGGA	TCCGGATCTT	AGCGACGGGT	CATGGTCAAC	GGTCAGTAGT	GAGGCCAACG	CGGAGGATGT	GACCTCCCCC	TCGGACCCCT	AGGCCTAGAA	TCGCTGCCCA	GTACCAGTTG	CCAGTCATCA	CTCCGGTTGC	GCCTCTTACA												
+2	V	C	C	S	M	S	Y	S	W	T	G	A	L	V	T	P	C	A	A	E	E	Q	K	L	P	I		
5521	CGTGTGCTGC	TCAATGTCTT	ACTCTTGGAC	AGGCGCACTC	GTCACCCCGT	GCGCCGCGGA	AGAACAGAAA	CTGCCCATCA	GCACACGACG	AGTTACAGAA	TGAGAACCTG	TCCGCGTGAG	CAGTGGGGCA	CGCGGCGCCT	TCTTGTCTTT	GACGGGTAGT												
+2	N	A	L	S	N	S	L	L	R	H	H	N	L	V	Y	S	T	T	S	R	S	A	C	Q	R	Q	K	
5601	ATGCACTAAG	CAACTCGTTG	CTACGTCACC	ACAATTTGGT	GTATTCCACC	ACCTCACGCA	GTGCTTGCCA	AAGGCAGAAG	TACGTGATTC	GTTGAGCAAC	GATGCAGTGG	TGTTAAACCA	CATAAGGTGG	TGGAGTGCCT	CACGAACGGT	TTCCGTCTTC												
+2	K	V	T	F	D	R	L	Q	V	L	D	S	H	Y	Q	D	V	L	K	E	V	K	A	A	A	S	K	
5681	AAAGTCACAT	TTGACAGACT	GCAAGTTCTG	GACAGCCATT	ACCAGGACGT	ACTCAAGGAG	GTAAAGCAG	CGGCGTCAAA	TTTCAGTGTA	AACTGTCTGA	CGTTCAAGAC	CTGTCCGTAA	TGGTCT															



## FIGURE 5 - Page 6

+2 R L I V F P D L G V R V C E K M A L Y D V V T K L P  
 6001 TCGTCTCATC GTGTTCCCCG ATCTGGGCGT GCGCGTGTGC GAAAAGATGG CTTTGTACGA CGTGGTTACA AAGCTCCCT  
 AGCAGAGTAG CACAAGGGGC TAGACCCGCA CGCGCACACG CTTTCTACC GAAACATGCT GCACCAATGT TTCGAGGGGA

---

+2 L A V M G S S Y G F Q Y S P G Q R V E F L V Q A W K S  
 EcoRI  
 ~~~~~  
 6081 TGGCCGTGAT GGGAAGCTCC TACGGATTCC AATACTCACC AGGACAGCGG GTTGAATTCC TCGTGCAAGC GTGGAAGTCC
 ACCGGCACTA CCCTTCGAGG ATGCTTAAGG TTATGAGTGG TCCTGTGCCC CAACTTAAGG AGCACGTTCC CACCTTCAGG

+2 K K T P M G F S Y D T R C F D S T V T E S D I R T E E
 6161 AAGAAAACCC CAATGGGGTT CTCGTATGAT ACCCGTGTCT TTGACTCCAC AGTCACTGAG AGCGACATCC GTACGGAGGA
 TTCTTTTGGG GTTACCCCAA GAGCATACTA TGGGCGACGA AACTGAGGTG TCAGTGACTC TCGTGTAGG CATGCCTCT

+2 A I Y Q C C D L D P Q A R V A I K S L T E R L Y V G
 6241 GGCAATCTAC CAATGTTGTG ACCTCGACCC CCAAGCCCGC GTGGCCATCA AGTCCCTCAC CGAGAGGCTT TATGTTGGGG
 CCGTTAGATG GTTACAACAC TGGAGCTGGG GGTTCGGGCG CACCGGTAGT TCAGGGAGTG GCTCTCCGAA ATACAACCC

+2 G P L T N S R G E N C G Y R R C R A S G V L T T S C G
 6321 GCCCTCTTAC CAATTCAAGG GGGGAGAACT GCGGCTATCG CAGGTGCCGC GCGAGCGGCG TACTGACAAC TAGCTGTGGT
 CGGGAGAATG GTTAAGTTC CCCCTCTTGA CGCCGATAGC GTCCACGGCG CGCTCGCCGC ATGACTGTTG ATCGACACCA

+2 N T L T C Y I K A R A A C R A A G L Q D C T M L V C G
 6401 AACACCCTCA CTTGCTACAT CAAGGCCCGG GCAGCCTGTC GAGCCGCAGG GCTCCAGGAC TGCACCATGC TCGTGTGTGG
 TTGTGGGAGT GAACGATGTA GTTCCGGGCC CGTCGGACAG CTCGGCGTCC CGAGGTCTCTG ACGTGGTACG AGCACACACC

+2 D D L V V I C E S A G V Q E D A A S L R A F T E A M
 6481 CGACGACTTA GTCGTTATCT GTGAAAGCGC GGGGGTCCAG GAGGACGCGG CGAGCCTGAG AGCCTTCACG GAGGCTATGA
 GCTGCTGAAT CAGCAATAGA CACTTTCGCG CCCCCAGGTC CTCCTGCGCC GCTCGGACTC TCGAAGTGC CTCGGATACT

+2 T R Y S A P P G D P P Q P E Y D L E L I T S C S S N V
 6561 CCAGGTACTC CGCCCCCCT GGGGACCCCC CACAACCAGA ATACGACTTG GAGCTCATAA CATCATGCTC CTCCAACGTG
 GGTCCATGAG GCGGGGGGGA CCCCTGGGGG GTGTTGGTCT TATGCTGAAC CTCGAGTATT GTAGTACGAG GAGGTTGCAC

+2 S V A H D G A G K R V Y Y L T R D P T T P L A R A A W
 6641 TCAGTCGCCC ACGACGGCGC TGGAAAGAGG GTCTACTACC TCACCCGTGA CCCTACAACC CCCCTCGCGA GAGCTGCGTG
 AGTCAGCGGG TGCTGCCGCG ACCTTCTCCT CAGATGATGG AGTGGGCACT GGGATGTTGG GGGGAGCGCT CTCGACGCAC

+2 E T A R H T P V N S W L G N I I M F A P T L W A R M
 6721 GGAGACAGCA AGACACACTC CAGTCAATTC CTGGCTAGGC AACATAATCA TGTTTGCCCC CACACTGTGG GCGAGGATGA
 CCTCTGTCGT TCTGTGTGAG GTCAGTTAAG GACCGATCCG TTGTATTAGT ACAAACGGGG GTGTGACACC CGCTCCTACT

+2 I L M T H F F S V L I A R D Q L E Q A L D C E I Y G A
 6801 TACTGATGAC CCATTTCTTT AGCGTCCTTA TAGCCAGGGA CCAGCTTGAA CAGGCCCTCG ATTGCGAGAT CTACGGGGCC
 ATGACTACTG GGTAAAGAAA TCGCAGGAAT ATCGGTCCCT GGTCAACTT GTCCGGGAGC TAACGCTCTA GATGCCCGGG

+2 C Y S I E P L D L P P I I Q R L H G L S A F S L H S Y
 6881 TGCTACTCCA TAGAACCCTT GGATCTACCT CCAATCATTC AAAGACTCCA TGGCCTCAGC GCATTTTCAC TCCACAGTTA
 ACGATGAGGT ATCTTGGTGA CCTAGATGGA GGTTAGTAAG TTTCTGAGGT ACCGGAGTCG CGTAAAAGTG AGGTGTCAAT

+2 S P G E I N R V A A C L R K L G V P P L R A W R H R
 6961 CTCTCCAGGT GAAATCAATA GGGTGGCCGC ATGCTCAGA AAAGTGGGG TACCGCCCTT GCGAGCTTGG AGACACCGGG
 GAGAGGTCCA CTTTAGTTAT CCCACCGGCG TACGGAGTCT TTTGAACCC ATGGCGGGAA CGCTCGAACC TCTGTGGCCC

+2 A R S V R A R L L A R G G R A A I C G K Y L F N W A V
 7041 CCCGAGCGT CCGCGCTAGG CTTCTGGCCA GAGGAGGCAG GGCTGCCATA TGTGGCAAGT ACCTCTTCAA CTGGGCAGTA
 GGGCCTCGCA GCGCGATCC GAAGACCGGT CTCCTCCGTC CCGACGGTAT ACACGGTTCA TGGAGAAGTT GACCCGTCAT

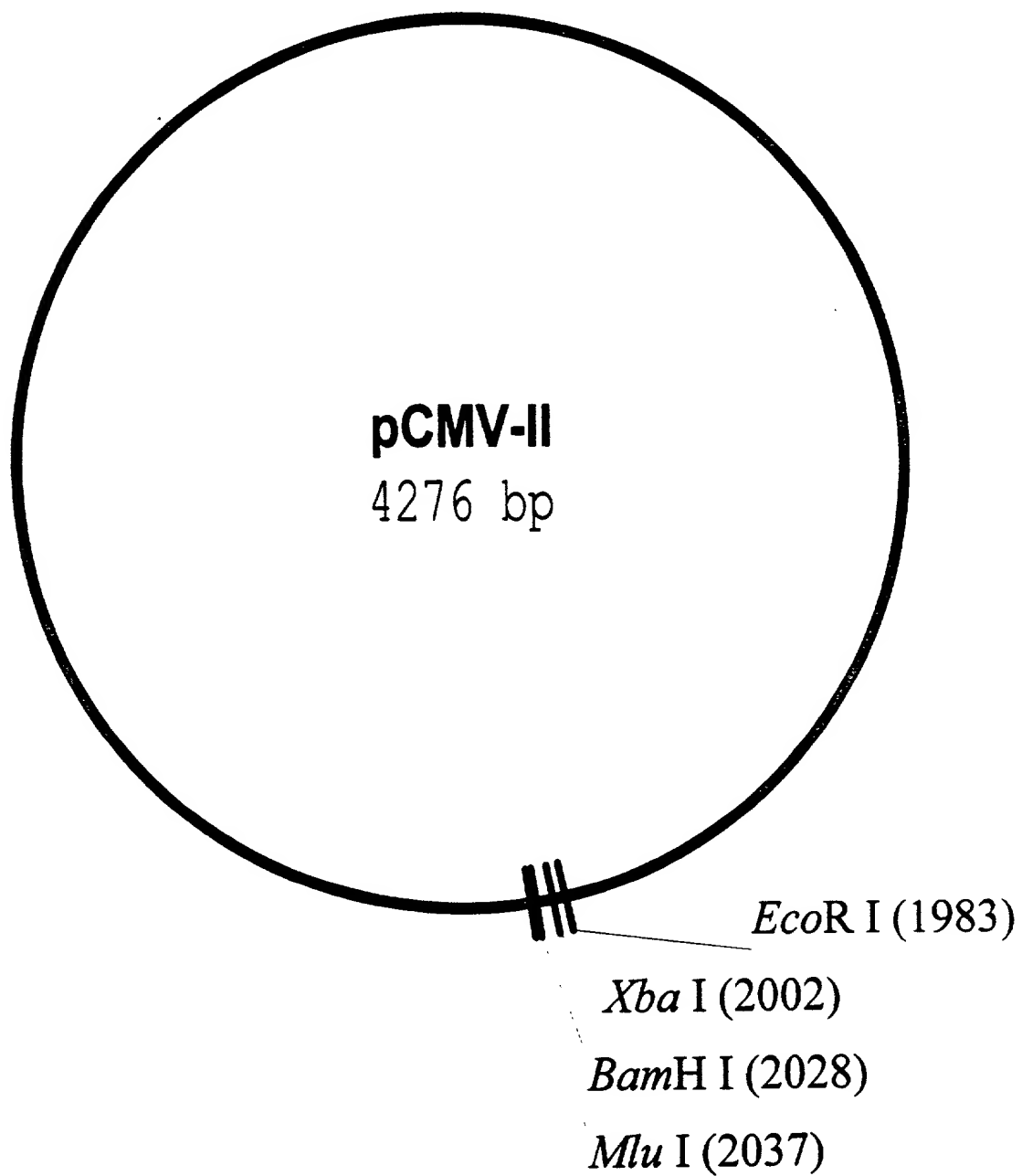
FIGURE 5 - Page 7

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|------|----|-------------|-------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------|------------|------------|-------------|------------|---|---|---|---|---|---|---|---|---|---|
| | +2 | R | T | K | L | P | I | A | A | G | Q | L | D | L | S | G | W | F | T | A | G | Y | S | G | | | |
| 7121 | | AGAACAAAGC | TCAAACAC | TCCAATAGCG | GCCGCTGGCC | AGCTGGACTT | GTCGGGCTGG | TTCACGGCTG | GCTACAGCGG | TCTTGTTCG | AGTTTGAGTG | AGGTTATCGC | CGGCGACCGG | TCGACCTGAA | CAGGCCGACC | AAGTGCCGAC | CGATGTCGCC | | | | | | | | | | |
| | +2 | G | D | I | Y | H | S | V | S | H | A | R | P | R | W | I | W | F | C | L | L | L | L | A | A | G | V |
| 7201 | | GGGAGACATT | TATCACAGCG | TGTCATGTC | CCGGCCCCGC | TGGATCTGGT | TTTGCCTACT | CCTGCTTGCT | GCAGGGGTAG | CCCTCTGTAA | ATAGTGTGCG | ACAGAGTACG | GGCCGGGGCG | ACCTAGACCA | AAACGGATGA | GGACGAACGA | CGTCCCCATC | | | | | | | | | | |
| | +2 | G | I | Y | L | L | P | N | R | | | | | | | | | | | | | | | | | | |
| 7281 | | GCATCTACCT | CCTCCCCAAC | CGATGAAGGT | TGGGGTAAAC | ACTCCGGCCT | AAAAAAAAAA | AAAAATCTAG | AAAGGCGCGG | CGTAGATGGA | GGAGGGGTG | GCTACTTCCA | ACCCCATTTG | TGAGGCCGGA | TTTTTTTTTT | TTTTTAGATC | TTTCCGCGCG | | | | | | | | | | |
| | | | BamHI | | MluI | | | | | | | | | | | | | | | | | | | | | | |
| 7361 | | CAAGATATCA | AGGATCCACT | ACGCGTTAGA | GCTCGCTGAT | CAGCCTCGAC | TGTGCCTTCT | AGTTGCCAGC | CATCTGTTGT | GTTCTATAGT | TCCTAGGTGA | TGCGCAATCT | CGAGCGACTA | GTCGGAGCTG | ACACGGAAGA | TCAACGGTGC | GTAGACAACA | | | | | | | | | | |
| 7441 | | TTGCCCTCC | CCCCTGCCTT | CCTTGACCCT | GGAAGGTGCC | ACTCCCACTG | TCCTTTCCTA | ATAAAATGAG | GAAATTGCAT | AACGGGGAGG | GGGCACGGAA | GGAAGTGGGA | CCTTCCACGG | TGAGGGTGAC | AGGAAAGGAT | TATTTTACTC | CTTTAACGTA | | | | | | | | | | |
| 7521 | | CGCATTGTCT | GAGTAGGTGT | CATTCTATTC | TGGGGGGTGG | GGTGGGGCAG | GACAGCAAGG | GGGAGGATTG | GGAAGACAAT | GCGTAACAGA | CTCATCCACA | GTAAGATAAG | ACCCCCACC | CCACCCGTC | CTGTCTGTCC | CCCTCCTAAC | CCTTCTGTTA | | | | | | | | | | |
| 7601 | | AGCAGGCATG | CTGGGGAGCT | CTTCCGCTTC | CTCGCTCACT | GACTCGTGCG | GCTCGGTCGT | TCGGCTGCGG | CGAGCGGTAT | TCGTCCGTAC | GACCCCTCGA | GAAGGCGAAG | GAGCGAGTGA | CTGAGCGACG | CGAGCCAGCA | AGCCGACGCC | GCTCGCCATA | | | | | | | | | | |
| 7681 | | CAGCTCACTC | AAAGGCGGTA | ATACGGTTAT | CCACAGAATC | AGGGGATAAC | GCAGGAAAGA | ACATGTGAGC | AAAAGGCCAG | GTCGAGTGAG | TTTCCGCCAT | TATGCCAATA | GGTGTCTTAG | TCCCCTATTG | CGTCCTTTCT | TGTACACTCG | TTTCCGGTTC | | | | | | | | | | |
| 7761 | | CAAAAGGCCA | GGAACCGTAA | AAAGGCCGCG | TTGCTGGCGT | TTTTCCATAG | GCTCCGCCCC | CCTGACGAGC | ATCACAAAAA | GTTTTCCGGT | CCTTGGCATT | TTTCCGGCGC | AACGACCGCA | AAAAGGTATC | CGAGGCGGGG | GGACTGCTCG | TAGTGTTTTT | | | | | | | | | | |
| 7841 | | TCGACGCTCA | AGTCAGAGGT | GGCGAAACCC | GACAGGACTA | TAAAGATACC | AGGCGTTTCC | CCCTGGAAGC | TCCCTCGTGC | AGCTGCGAGT | TCAGTCTCCA | CCGCTTTGGG | CTGTCTTGAT | ATTTCTATGG | TCCGCAAAGG | GGGACCTTCG | AGGGAGCACG | | | | | | | | | | |
| 7921 | | GCTCTCCTGT | TCCGACCCCTG | CCGCTTACCG | GATACCTGTC | CGCCTTTCTC | CCTTCGGGAA | GCGTGGCGCT | TTCTCAATGC | CGAGAGGACA | AGGCTGGGAC | GGCGAATGGC | CTATGGACAG | GCGGAAAGAG | GGAAGCCCTT | CGCACC CGGA | AAGAGTTACG | | | | | | | | | | |
| 8001 | | TCACGCTGTA | GGTATCTCAG | TTCGGTGTAG | GTCTGTCGCT | CCAAGCTGGG | CTGTGTGCAC | GAACCCCCCG | TTCAGCCCCG | AGTGCGACAT | CCATAGAGTC | AAGCCACATC | CAGCAAGCGA | GGTTCGACCC | GACACACGTG | CTTGGGGGGC | AAGTCGGGCT | | | | | | | | | | |
| 8081 | | CCGCTGCGCC | TTATCCGGTA | ACTATCGTCT | TGAGTCCAAC | CCGGTAAGAC | ACGACTTATC | GCCACTGGCA | GCAGCCACTG | GGCGACGCGG | AATAGGCCAT | TGATAGCAGA | ACTCAGGTTG | GGCCATTCTG | TGCTGAATAG | CGGTGACCGT | CGTCGGTGAC | | | | | | | | | | |
| 8161 | | GTAACAGGAT | TAGCAGAGCG | AGGTATGTAG | GCGGTGCTAC | AGAGTTCTTG | AAGTGGTGGC | CTAACTACGG | CTAACTAGAG | CATTGTCCTA | ATCGTCTCGC | TCCATACATC | CGCCACGATG | TCTCAAGAAC | TTCACCACCG | GATTGATGCC | GATGTGATCT | | | | | | | | | | |
| 8241 | | AGGACAGTAT | TTGGTATCTG | CGCTCTGCTG | AAGCCAGTTA | CCTTCGGAAA | AAGAGTTGGT | AGCTCTTGAT | CCGGCAAACA | TCCTGTCATA | AACCATAGAC | GCGAGACGAC | TTCCGGTCAAT | GGAAGCCTTT | TTCTCAACCA | TCGAGAACTA | GGCCGTTTGT | | | | | | | | | | |
| 8321 | | AACCAACCGCT | GGTAGCGGTG | GTTTTTTTGT | TTGCAAGCAG | CAGATTACGC | GCAGAAAAAA | AGGATCTCAA | GAAGATCCTT | TTGGTGGCGA | CCATCGCCAC | CAAAAAACA | AACGTTTCGT | GTCTAATGCG | CGTCTTTTTT | TCCTAGAGTT | CTTCTAGGAA | | | | | | | | | | |
| 8401 | | TGATCTTTTC | TACGGGGTCT | GACGCTCAGT | GGAACGAAAA | CTCAC | | | | | | | | | | | | | | | | | | | | | |

FIGURE 5 - Page 8

| | | | | | | | | |
|------|--------------------------|---------------------------|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 8481 | ATCTTCACCT
TAGAAGTGGG | AGATCCITTT
TCTAGGAAAA | AAATTA AAAA
TTTAATTTTT | TGAAGTTTTA
ACTTCAAAAT | AATCAATCTA
TTAGTTAGAT | AAGTATATAT
TTCATATATA | GAGTAAACTT
CTCATTGAA | GGTCTGACAG
CCAGACTGTC |
| 8561 | TTACCAATGC
AATGGTTACG | TTAATCAGTG
AATTAGTCAC | AGGCACCTAT
TCCGTGGATA | CTCAGCGATC
GAGTCGCTAG | TGTCTATTTT
ACAGATAAAG | GTTCATCCAT
CAAGTAGGTA | AGTTGCCTGA
TCAACGGACT | CTCCCGTGCG
GAGGGGCAGC |
| 8641 | TGTAGATAAC
ACATCTATTG | TACGATACGG
ATGCTATGCC | GAGGGCTTAC
CTCCCGAATG | CATCTGGCCC
GTAGACCGGG | CAGTGCTGCA
GTCACGACGT | ATGATACCGC
TACTATGGCG | GAGACCCACG
CTCTGGGTGC | CTCACCGGCT
GAGTGGCCGA |
| 8721 | CCAGATTTAT
GGTCTAAATA | CAGCAATAAA
GTCGTTATTT | CCAGCCAGCC
GGTCGGTCGG | GGAAGGGCCG
CCTTCCCGGC | AGCGCAGAAG
TCGCGTCTTC | TGGTCTTGCA
ACCAGGACGT | ACTTTATCCG
TGAAATAGGC | CCTCCATCCA
GGAGGTAGGT |
| 8801 | GTCTATTAAT
CAGATAATTA | TGTTGCCGGG
ACAACGGCCC | AAGCTAGAGT
TTCGATCTCA | AAGTAGTTCG
TTCATCAAGC | CCAGTTAATA
GGTCAATTAT | GTTTGCGCAA
CAAACGCGTT | CGTTGTTGCC
GCAACAACGG | ATTGCTACAG
TAACGATGTC |
| 8881 | GCATCGTGGT
CGTAGCACCA | GTCACGCTCG
CAGTGCAGAC | TCGTTTGGA
AGCAAACCAT | TGGCTTCATT
ACCGAAGTAA | CAGCTCCGGT
GTCGAGGCCA | TCCCAACGAT
AGGGTTGCTA | CAAGGCGAGT
GTTCCGCTCA | TACATGATCC
ATGTACTAGG |
| 8961 | CCCATGTTGT
GGGTACAACA | GCAAAAAAGC
CGTTTTTTCG | GGTTAGCTCC
CCAATCGAGG | TTCGGTCTCT
AAGCCAGGAG | CGATCGTTGT
GCTAGCAACA | CAGAAGTAAG
GTCTTCATT | TGGCCGCAG
AACC GGCGTC | TGTTATCACT
ACAATAGTGA |
| 9041 | CATGGTTATG
GTACCAATAC | GCAGCACTGC
CGTCGTGACG | ATAATTCTCT
TATTAAGAGA | TACTGTCATG
ATGACAGTAC | CCATCCGTAA
GGTAGGCATT | GATGCTTTTC
CTACGAAAAG | TGTGACTGGT
AACTGACCA | GAGTACTCAA
CTCATGAGTT |
| 9121 | CCAAGTCATT
GGTTCAGTAA | CTGAGAATAG
GACTCTTATC | TGTATGCGGC
ACATACGCCG | GACCGAGTTG
CTGGCTCAAC | CTCTTGCCCG
GAGAACGGGC | GCGTCAATAC
CGCAGTTATG | GGGATAATAC
CCCTATTATG | CGCGCCACAT
GCGCGGTGTA |
| 9201 | AGCAGAACTT
TCGTCTTGAA | TAAAAAGTGCT
ATTTTCACGA | CATCATTGGA
GTAGTAACCT | AAACGTTCTT
TTTGCAAGAA | CGGGGCGAAA
GCCCCGCTTT | ACTCTCAAGG
TGAGAGTTCC | ATCTTACCGC
TAGAATGGCG | TGTTGAGATC
ACAACTCTAG |
| 9281 | CAGTTCGATG
GTCAAGCTAC | TAACCCACTC
ATTGGGTGAG | GTGCACCCAA
CACGTGGGTT | CTGATCTTCA
GACTAGAAGT | GCATCTTTTA
CGTAGAAAAT | CTTTCACCAG
GAAAGTGGTC | CGTTTCTGGG
GCAAAGACCC | TGAGCAAAAA
ACTCGTTTTT |
| 9361 | CAGGAAGGCA
GTCCTTCCGT | AAATGCCGCA
TTTACGGCGT | AAAAAGGGAA
TTTTTCCCTT | TAAGGGCGAC
ATTCCCGCTG | ACGGAAATGT
TGCCTTTACA | TGAATACTCA
ACTTATGAGT | TACTCTTCCT
ATGAGAAGGA | TTTTCAATAT
AAAAGTTATA |
| 9441 | TATTGAAGCA
ATAACTTCGT | TTTATCAGGG
AAATAGTCCC | TTATTGTCTC
AATAACAGAG | ATGAGCGGAT
TACTCGCCTA | ACATATTTGA
TGTATAAACT | ATGTATTTAG
TACATAAATC | AAAAATAAAC
TTTTTATTTG | AAATAGGGGT
TTTATCCCCA |
| 9521 | TCCGCGCACA
AGGCGCGTGT | TTTCCCCGAA
AAAGGGGCTT | AAGTGCCACC
TTCACGGTGG | TGACGTCTAA
ACTGCAGATT | GAAACCATTA
CTTTGGTAAT | TTATCATGAC
AATAGTACTG | ATTAACCTAT
TAATTGGATA | AAAAATAGGC
TTTTTATCCG |
| 9601 | GTATCACGAG
CATAGTGCTC | GCCCTTTCGT
CGGGAAAGCA | C
G | | | | | |

FIGURE 6



00221473-13200

FIGURE 7 - Page 1

1 TCGCGCGTTT CGGTGATGAC GGTGAAAACC TCTGACACAT GCAGCTCCCG GAGACGGTCA CAGCTTGTCT GTAAGCGGAT
AGCGCGCAAA GCCACTACTG CCACTTTTGG AGACTGTGTA CGTCGAGGGC CTCTGCCAGT GTCGAACAGA CATTCGCCTA

81 GCCGGGAGCA GACAAGCCCC TCAGGGCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCTGG CTTAACTATG CGGCATCAGA
CGGCCCTCGT CTGTTCCGGC AGTCCCGCGC AGTCGCCCAC AACC GCCCAC AGCCCCGACC GAATTGATAC GCCGTAGTCT

161 GCAGATTGTA CTGAGAGTGC ACCATATGAA GCTTTTTGCA AAAGCCTAGG CCTCCAAAAA AGCCTCCTCA CTAATTCTGG
CGTCTAACAT GACTCTCACG TGGTATACTT CGAAAAACGT TTTTCGGATCC GGAGGTTTTT TCGGAGGAGT GATGAAGACC

241 AATAGCTCAG AGGCCGAGGC GGCCTCGGCC TCTGCATAAA TAAAAAAAT TAGTCAGCCA TGGGGCGGAG AATGGGCGGA
TTATCGAGTC TCCGGCTCCG CCGGAGCCGG AGACGTATTT ATTTTTTTTA ATCAGTCGGT ACCCCGCCCTC TTACCCGCCCT

321 ACTGGGCGGG GAGGGAATTA TTGGCTATTG GCCATTGCAT ACGTTGTATC TATATCATAA TATGTACATT TATATTGGCT
TGACCCGCC CTCCCTTAAT AACCGATAAC CGGTAACGTA TGCAACATAG ATATAGTATT ATACATGTAA ATATAACCGA

401 CATGTCCAAT ATGACCGCCA TGTGACATT GATTATTGAC TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT
GTACAGGTTA TACTGGCGGT ACAACTGTAA CTAATAACTG ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA

481 AGCCCATATA TGGAGTTCGG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCCAACGACC CCCGCCATT
TCGGGTATAT ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC GGGTTGCTGG GGGCGGGTAA

561 GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT
CTGCAGTTAT TACTGCATAC AAGGGTATCA TTGCGGTTAT CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

641 AAAGTGGCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTCCGCCC CCTATTGACG TCAATGACGG TAAATGGCCC
TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCAGGCGGG GGATAACTGC AGTTACTGCC ATTTACCGGG

721 GCCTGGCATT ATGCCAGTA CATGACCTTA CGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA TCGCTATTAC
CGGACCGTAA TACGGGTCAT GTACTGGAAT GCCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT AGCGATAATG

801 CATGGTGATG CGGTTTTGGC AGTACACCAA TGGGCGTGGA TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA
GTACCACTAC GCCAAAACCG TCATGTGGTT ACCCGCACCT ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT

881 TTGACGTCAA TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA ATAACCCCGC CCCGTTGACG
AACTGCAGTT ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT TATTGGGGCG GGGCAACTGC

961 CAAATGGGCG GTAGGCGTGT ACGGTGGGAG GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG
GTTTACCCGC CATCCGCACA TGCCACCCTC CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

1041 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC TCCGCGGCCG GGAACGGTGC ATTGGAACGC
GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTCGG AGGCGCCGGC CTTTGCCACG TAACCTTGCG

1121 GGATTCCCCG TGCCAAGAGT GACGTAAGTA CCGCCTATAG ACTCTATAGG CACACCCCTT TGGCTCTTAT GCATGCTATA
CCTAAGGGGC ACGGTTCTCA CTGCATTCAT GCGGATATC TGAGATATCC GTGTGGGGAA ACCGAGAATA CGTACGATAT

1201 CTGTTTTTGG CTTGGGGCCT ATACACCCCC GCTCCTTATG CTATAGGTGA TGGTATAGCT TAGCCTATAG GTGTGGGTTA
GACAAAAACC GAACCCCGGA TATGTGGGGG CGAGGAATAC GATATCCACT ACCATATCGA ATCGGATATC CACACCCAAT

1281 TTGACCATTA TTGACCACTC CCCTATTGGT GACGATACTT TCCATTACTA ATCCATAACA TGGCTCTTTG CCACAACAT
AACTGGTAAT AACTGGTGAG GGGATAACCA CTGCTATGAA AGGTAATGAT TAGGTATTGT ACCGAGAAAC GGTGTTGATA

1361 CTCTATTGGC TATATGCCAA TACTCTGTCC TTCAGAGACT GACACGGACT CTGTATTTTT ACAGGATGGG GTCCATTTAT
GAGATAACCG ATATACGGTT ATGAGACAGG AAGTCTCTGA CTGTGCCTGA GACATAAAAA TGTCCTACCC CAGGTAAATA

1441 TATTTACAAA TTCACATATA CAACAACGCC GTCCCCCGTG CCCGCAGTTT TTATTAAACA TAGCGTGCGA TCTCCGACAT
ATAAATGTTT AAGTGTATAT GTTGTTCGG CAGGGGGCAC GGGCGTCAAA AATAATTTGT ATCGCACCTC AGAGGCTGTA

FIGURE 7 - Page 2

1521 CTCGGGTACG TGTTCGGAC ATGGGCTCTT CTCCGGTAGC GCGGGAGCTT CCACATCCGA GCCCTGGTCC CATCCGTCCA
GAGCCCATGC ACAAGGCCTG TACCCGAGAA GAGGCCATCG CCGCCTCGAA GGTGTAGGCT CGGGACCAGG GTAGGCAGGT

1601 GCGGCTCATG GTCGCTCGGC AGCTCCTTGC TCCTAACAGT GGAGGCCAGA CTTAGGCACA GCACAATGCC CACCACCACC
CGCCGAGTAC CAGCGAGCCG TCGAGGAACG AGGATTGTCA CCTCCGGTCT GAATCCGTGT CGTGTACCG GTGGTGGTGG

1681 AGTGTGCCGC ACAAGGCCGT GCGGGTAGGG TATGTGTCTG AAAATGAGCT CGGAGATTGG GCTCGCACCT GGACGCAGAT
TCACACGGCG TGTTCGGCA CCGCCATCCC ATACACAGAC TTTTACTCGA GCCTCTAACC CGAGCGTGA CCTGCGTCTA

1761 GGAAGACTTA AGGCAGCGGC AGAAGAAGAT GCAGGCAGCT GAGTTGTTGT ATTCTGATAA GAGTCAGAGG TAACTCCCGT
CCTTCTGAAT TCCGTCGCCG TCTTCTTCTA CGTCCGTCGA CTCAACAACA TAAGACTATT CTCAGTCTCC ATTGAGGGCA

1841 TGCGGTGCTG TTAACGGTGG AGGGCAGTGT AGTCTGAGCA GTACTCGTTG CTGCCGCGCG CGCCACCAGA CATAATAGCT
ACGCCACGAC AATTGCCACC TCCCGTCACA TCAGACTCGT CATGAGCAAC GACGGCGCGC GCGGTGGTCT GTATTATCGA

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1921 GACAGACTAA CAGACTGTTT CTTTCCATGG GTCTTTTCTG CAGTCACCGT CGTCGACCTA AGAATTCAGA CTCGAGCAAG  
CTGTCTGATT GTCTGACAAG GAAAGGTACC CAGAAAAGAC GTCAGTGGCA GCAGCTGGAT TCTTAAGTCT GAGCTCGTTC

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XbaI                      BamHI              MluI  
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2001 TCTAGAAAGG CGCGCCAAGA TATCAAGGAT CCACTACGCG TTAGAGCTCG CTGATCAGCC TCGACTGTGC CTTCTAGTTG
AGATCTTTCC GCGCGTTTCT ATAGTTTCTA GGTGATGCGC AATCTCGAGC GACTAGTCGG AGCTGACACG GAAGATCAAC

2081 CCAGCCATCT GTTGTGTTGCC CCTCCCCCGT GCCTTCCTTG ACCCTGGAAG GTGCCACTCC CACTGTCTTT TCCTAATAAA
GGTCGGTAGA CAACAAACGG GGAGGGGGCA CGGAAGGAAC TGGGACCTTC CACGGTGAGG GTGACAGGAA AGGATTATTT

2161 ATGAGGAAAT TGCATCGCAT TGCTGAGTA GGTGTCTTTC TATTCTGGGG GGTGGGGTGG GGCAGGACAG CAAGGGGGAG
TACTCCTTTA ACGTAGCGTA ACAGACTCAT CCACAGTAAG ATAAGACCCC CCACCCACC CCGTCTGTG GTTCCCCCTC

2241 GATTGGGAAG ACAATAGCAG GCATGCTGGG GAGCTCTTCC GCTTCCTCGC TCACTGACTC GCTGCGCTCG GTCGTTCCGC
CTAACCTTTC TGTTATCGTC CGTACGACCC CTCGAGAAGG CGAAGGAGCG AGTACTGAG CGACGCGAGC CAGCAAGCCG

2321 TGCGGCGAGC GGTATCAGCT CACTCAAAGG CGGTAATACG GTTATCCACA GAATCAGGGG ATAACGCAGG AAAGAACATG
ACGCCGCTCG CCATAGTCGA GTGAGTTTCC GCCATTATGC CAATAGGTGT CTTAGTCCCC TATTGCGTCC TTTCTGTAC

2401 TGAGCAAAAAG GCCAGCAAAA GGCCAGGAAC CGTAAAAAGG CCGCGTTGCT GCGGTTTTTC CATAGGCTCC GCCCCCTGA
ACTCGTTTTT CGGTCTTTTT CCGTCTCTTG GCATTTTTTC GGCGCAACGA CCGCAAAAAG GTATCCGAGG CGGGGGGACT

2481 CGAGCATCAC AAAAATCGAC GCTCAAGTCA GAGGTGGCGA AATCCGACAG GACTATAAAG ATACCAGGCG TTTCCCCCTG
GCTCGTAGTG TTTTLAGCTG CGAGTTTCACT CTCCACCGCT TTGGGCTGTC CTGATATTTT TATGGTCCGC AAAGGGGGAC

2561 GAAGCTCCCT CGTGCGCTCT CCTGTTCGA CCCTGCCGCT TACCGGATAC CTGTCCGCTT TTCTCCCTTC GGAAGCGTG
CTTCGAGGGA GCACGCGAGA GGACAAGGCT GGGACGGCGA ATGGCCTATG GACAGGCGGA AAGAGGGGAG CCCTTCGCAC

2641 GCGCTTTTCT AATGCTCAGC CTGTAGGTAT CTCAGTTCGG TGTAGGTCGT TCGCTCCAAG CTGGGCTGTG TGCACGAACC
CGCGAAAGAG TTACGAGTGC GACATCCATA GAGTCAAGCC ACATCCAGCA AGCGAGGTTT GACCCGACAC ACGTGCTTGG

2721 CCCCCTTTCAG CCCGACCGCT GCGCCTTATC CGGTAACATAT CGTCTTGAGT CCAACCCGGT AAGACACGAC TTATCGCCAC
GGGGCAAGTC GGGCTGGCGA CGCGGAATAG GCCATTGATA GCAGAACTCA GGTGTTGGCA TTCTGTGCTG AATAGCGGTG

2801 TGGCAGCAGC CACTGGTAAC AGGATTAGCA GAGCGAGGTA TGTAGGCGGT GCTACAGAGT TCTTGAAGTG GTGGCCTAAC
ACCGTCGTCG GTGACCATG TCCTAATCGT CTCGCTCCAT ACATCCGCCA CGATGTCTCA AGAACTTCAC CACCGGATTG

2881 TACGGCTACA CTAGAAGGAC AGTATTTGGT ATCTGCGCTC TGCTGAAGCC AGTTACCTTC GGAAAAAGAG TTGGTAGCTC
ATGCCGATGT GATCTTCTCTG TCATAAACCA TAGACGCGAG ACGACTTCGG TCAATGGAAG CCTTTTTCTC AACCATCGAG

FIGURE 7 - Page 3

2961 TTGATCCGGC AAACAAACCA CCGCTGGTAG CGGTGGTTTT TTTGTTTGCA AGCAGCAGAT TACGCGCAGA AAAAAAGGAT
AACTAGGCCG TTTGTTTGGT GGCGACCATC GCCACCAAAA AAACAAACGT TCGTCGTCTA ATGCGCGTCT TTTTTTCCTA

3041 CTCAAGAAGA TCCTTTGATC TTTTCTACGG GGTCTGACGC TCAGTGGAAC GAAAACCTAC GTTAAGGGAT TTTGGTCATG
GAGTTCTTCT AGGAACTAG AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTTGAGTG CAATTCCCTA AAACCAGTAC

3121 AGATTATCAA AAAGGATCTT CACCTAGATC CTTTTAAATT AAAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA
TCTAATAGTT TTTCTAGAA GTGGATCTAG GAAAATTTAA TTTTACTTC AAAATTTAGT TAGATTTCAT ATATACTCAT

3201 AACTTGGTCT GACAGTTACC AATGCTTAAT CAGTGAGGCA CCTATCTCAG CGATCTGTCT ATTTGCTTCA TCCATAGTTG
TTGAACCAGA CTGTCAATGG TTACGAATTA GTCACCTCCG GGATAGAGTC GCTAGACAGA TAAAGCAAGT AGGTATCAAC

3281 CCTGACTCCC CGTCGTGTAG ATAACACGA TACGGGAGGG CTTACCATCT GGCCCCAGTG CTGCAATGAT ACCGCGAGAC
GGACTGAGGG GCAGCACATC TATTGATGCT ATGCCCTCCC GAATGGTAGA CCGGGGTCAC GACGTTACTA TGGCGCTCTG

3361 CCACGCTCAC CGGCTCCAGA TTTATCAGCA ATAAACCAGC CAGCCGGAAG GGCCGAGCGC AGAAGTGGTC CTGCAACTTT
GGTGCGAGTG GCCGAGGTCT AAATAGTCGT TATTTGGTCG GTCGGCCTTC CCGGCTCGCG TCTTCACCAG GACGTTGAAA

3441 ATCCGCCTCC ATCCAGTCTA TTAATTGTTG CCGGGAAGCT AGAGTAAGTA GTTCGCCAGT TAATAGTTTG CGCAACGTTG
TAGGCGGAGG TAGGTCAGAT AATTAACAAC GGCCCTTCGA TCTCATTCTA CAAGCGGTCA ATTATCAAAC GCGTTGCAAC

3521 TTGCCATTGC TACAGGCATC GTGGTGTAC GTCGTCGTT TGGTATGGCT TCATTAGCT CCGGTTCCCA ACGATCAAGG
AACGGTAACG ATGTCCGTAG CACCACAGTG CGAGCAGCAA ACCATACCGA AGTAAGTCGA GGCCAAGGGT TGCTAGTTCC

3601 CGAGTTACAT GATCCCCCAT GTTGTGCAAA AAAGCGGTTA GTCCTTCGG TCCTCCGATC GTTGTGAGAA GTAAGTTGGC
GCTCAATGTA CTAGGGGGTA CAACACGTTT TTTGCGCAAT CGAGGAAGCC AGGAGGCTAG CAACAGTCTT CATTCAACCG

3681 CGCAGTGTTA TCACTCATGG TTATGGCAGC ACTGCATAAT TCTCTTACTG TCATGCCATC CGTAAGATGC TTTTCTGTGA
GCGTCACAAT AGTGAGTACC AATACCGTCG TGACGTATTA AGAGAATGAC AGTACGGTAG GCATTCTACG AAAAGACACT

3761 CTGGTGAGTA CTCAACCAAG TCATTCTGAG AATAGTGTAT GCGGCGACCG AGTTGCTCTT GCCCGGCGTC AATACGGGAT
GACCACTCAT GAGTTGGTTC AGTAAGACTC TTATCACATA CGCCGCTGGC TCAACGAGAA CGGGCCGCGAG TTATGCCCTA

3841 AATACCGCGC CACATAGCAG AACTTTAAAA GTGCTCATCA TTGGAAAACG TTCTTCGGGG CGAAAACCTCT CAAGGATCTT
TTATGGCGCG GTGTATCGTC TTGAAATTTT CACGAGTAGT AACCTTTTGC AAGAAGCCCC GCTTTTGAGA GTTCCTAGAA

3921 ACCGCTGTTG AGATCCAGTT CGATGTAAC CACTCGTGCA CCCAACTGAT CTTCAGCATC TTTTACTTTC ACCAGCGTTT
TGGCGACAAC TCTAGGTCAA GCTACATTGG GTGAGCACGT GGGTTGACTA GAAGTCGTAG AAAATGAAAG TGGTCGCAAA

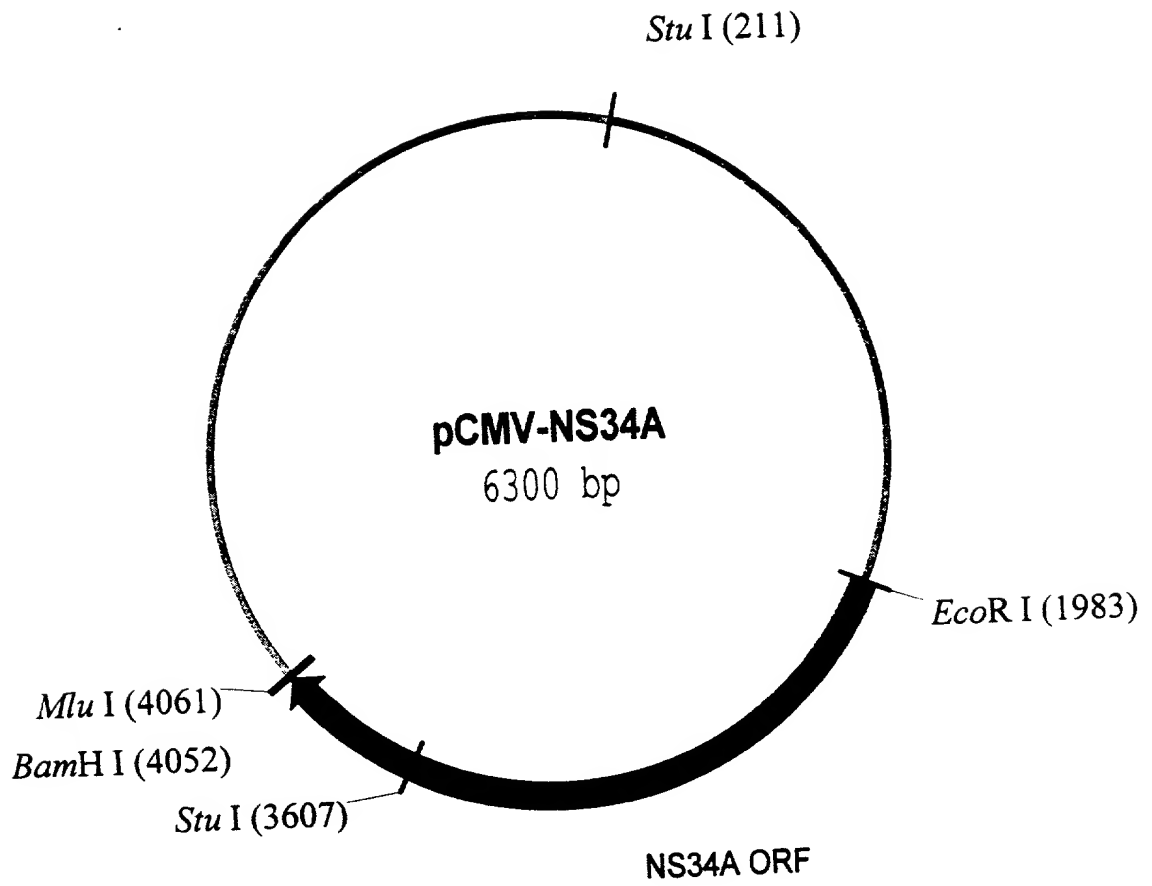
4001 CTGGGTGAGC AAAAACAGGA AGGCAAAATG CCGCAAAAAA GGAATAAGG GCGACACGGA AATGTTGAAT ACTCATACTC
GACCACTCG TTTTGTCTCT TCCGTTTTAC GCGTTTTTTT CCCTTATTCC CGCTGTGCCT TTACAACCTA TGAGTATGAG

4081 TTCCTTTTTC AATATTATTG AAGCATTTAT CAGGGTTATT GTCTCATGAG CGGATACATA TTTGAATGTA TTTAGAAAAA
AAGGAAAAAG TTATAATAAC TTCGTAAATA GTCCCAATAA CAGAGTACTC GCCTATGTAT AAACCTACAT AAATCTTTTT

4161 TAAACAAATA GGGGTTCCGC GCACATTTCC CCGAAAAGTG CCACCTGACG TCTAAGAAAC CATTATTATC ATGACATTAA
ATTTGTTTAT CCCCAAGGCG CGTGTAAGG GGCTTTTCAC GGTGGACTGC AGATTCTTTG GTAATAATAG TACTGTAATT

4241 CCTATAAAAA TAGGCGTATC ACGAGGCCCT TTCGTC
GGATATTTTT ATCCGCATAG TGCTCCGGGA AAGCAG

FIGURE 8



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FIGURE 9 - Page 1

1 TCGCGCGTTT CGGTGATGAC GGTGAAAACC TCTGACACAT GCAGCTCCCG
AGCGCGCAAA GCCACTACTG CCACTTTTGG AGACTGTGTA CGTCGAGGGC

51 GAGACGGTCA CAGCTTGTCT GTAAGCGGAT GCCGGGAGCA GACAAGCCCG
CTCTGCCAGT GTCGAACAGA CATTGCGCTA CGGCCCTCGT CTGTTGCGGC

101 TCAGGGCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCTGG CTTAACTATG
AGTCCCGCGC AGTCGCCAC AACCGCCAC AGCCCGGACC GAATTGATAC

151 CGGCATCAGA GCAGATTGTA CTGAGAGTGC ACCATATGAA GCTTTTGGCA
GCCGTAGTCT CGTCTAACAT GACTCTCAG TGGTATACTT CGAAAAACGT

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201 AAAGCCTAGG CCTCCAAAAA AGCCTCCTCA CTACTTCTGG AATAGCTCAG  
TTTCGGATCC GGAGGTTTTT TCGGAGGAGT GATGAAGACC TTATCGAGTC

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251 AGGCCGAGGC GGCCTCGGCC TCTGCATAAA TAAAAAAAT TAGTCAGCCA  
TCCGGCTCCG CCGGAGCCGG AGACGTATTT ATTTTTTTTA ATCAGTCGGT

---

301 TGGGGCGGAG AATGGGCGGA ACTGGGCGGG GAGGGAATTA TTGGCTATTG  
ACCCCGCCTC TTACCCGCCT TGACCCGCC CTCCCTTAAT AACCGATAAC

---

351 GCCATTGCAT ACGTTGTATC TATATCATAA TATGTACATT TATATTGGCT  
CGGTAACGTA TGCAACATAG ATATAGTATT ATACATGTAA ATATAACCGA

---

401 CATGTCCAAT ATGACCGCCA TGTGACATT GATTATTGAC TAGTTATTAA  
GTACAGGTTA TACTGGCGGT ACAACTGTAA CTAATACTG ATCAATAATT

---

451 TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA TGGAGTTCCG  
ATCATTAGTT AATGCCCCAG TAATCAAGTA TCGGGTATAT ACCTCAAGGC

---

501 CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCCAACGACC  
GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC GGGTTGCTGG

---

551 CCCGCCCAT GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA  
GGGCGGGTAA CTGCAGTTAT TACTGCATAC AAGGGTATCA TTGCGGTTAT

---

601 GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT AACTGCCCCA  
CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA TTTGACGGGT

---

651 CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTCCGCCC CCTATTGACG  
GAACCGTCAT GTAGTTCACA TAGTATACGG TTCAGGCGGG GGATAACTGC

---

701 TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCAGTA CATGACCTTA  
AGTTACTGCC ATTTACGGG CGGACCGTAA TACGGGTCAT GTACTGGAAT

---

751 CGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA TCGCTATTAC  
GCCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT AGCGATAATG

---

801 CATGGTGATG CGGTTTTGGC AGTACACCAA TGGGCGTGGA TAGCGGTTTG  
GTACCACTAC GCCAAAACCG TCATGTGGTT ACCCGCACCT ATCGCCAAAC

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851 ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA TGGGAGTTTG  
TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT AACTGCAGTT ACCCTCAAAC

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## FIGURE 9 - Page 2

901 TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA ATAACCCCGC  
 AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT TATTGGGGCG

---

951 CCCGTTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG GTCTATATAA  
 GGGCAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC CAGATATATT

---

1001 GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG CCATCCACGC  
 CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC GGTAGGTGCG

---

1051 TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC TCCGCGGGCCG  
 ACAAACTGG AGGTATCTTC TGTGGCCCTG GCTAGGTCGG AGGCGCCGGC

---

1101 GGAACGGTGC ATTGGAACGC GGATTCCCCG TGCCAAGAGT GACGTAAGTA  
 CCTTGCCACG TAACCTTGCG CCTAAGGGGC ACGGTTCTCA CTGCATTCTAT

---

1151 CCGCCTATAG ACTCTATAGG CACACCCCTT TGGCTCTTAT GCATGCTATA  
 GGC GGATATC TGAGATATCC GTGTGGGGAA ACCGAGAATA CGTACGATAT

---

1201 CTGTTTTTGG CTTGGGGCCT ATACACCCCC GCTCCTTATG CTATAGGTGA  
 GACAAAAACC GAACCCCGGA TATGTGGGGG CGAGGAATAC GATATCCACT

---

1251 TGGTATAGCT TAGCCTATAG GTGTGGGTGA TTGACCATTA TTGACCACTC  
 ACCATATCGA ATCGGATATC CACACCCAAT AACTGGTAAT AACTGGTGAG

---

1301 CCCTATTGGT GACGATACTT TCCATTACTA ATCCATAACA TGGCTCTTTG  
 GGGATAACCA CTGCTATGAA AGGTAATGAT TAGGTATTGT ACCGAGAAAC

---

1351 CCACAACAT CTCTATTGGC TATATGCCAA TACTCTGTCC TTCAGAGACT  
 GGTGTTGATA GAGATAACCG ATATACGGTT ATGAGACAGG AAGTCTCTGA

---

1401 GACACGGACT CTGTATTTTT ACAGGATGGG GTCCATTAT TATTTACAAA  
 CTGTGCCTGA GACATAAAAA TGTCCTACCC CAGGTAAATA ATAAATGTTT

---

1451 TTCACATATA CAACAACGCC GTCCCCCGTG CCCGCAGTTT TTATTAAACA  
 AAGTGATAT GTTGTTGCGG CAGGGGGCAC GGGCGTCAAA AATAATTTGT

---

1501 TAGCGTGGGA TCTCCGACAT CTCGGGTACG TGTTCGGGAC ATGGGCTCTT  
 ATCGCACCT AGAGGCTGTA GAGCCCATGC ACAAGGCCTG TACCCGAGAA

---

1551 CTCGGGTAGC GCGGAGCTT CCACATCCGA GCCCTGGTCC CATCGTCCA  
 GAGGCCATCG CCGCCTCGAA GGTGTAGGCT CGGGACCAGG GTAGGCAGGT

---

1601 GCGGCTCATG GTCGCTCGGC AGCTCCTTGC TCCTAACAGT GGAGGCCAGA  
 CGCCGAGTAC CAGCGAGCCG TCGAGGAACG AGGATTGTCA CCTCCGGTCT

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1651 CTTAGGCACA GCACAATGCC CACCACCACC AGTGTGCCGC ACAAGGCCGT  
 GAATCCGTGT CGTGTTACGG GTGGTGGTGG TCACACGGCG TGTTCGGCA

---

1701 GGCGGTAGGG TATGTGTCTG AAAATGAGCT CGGAGATTGG GCTCGCACCT  
 CCGCCATCCC ATACACAGAC TTTTACTCGA GCCTCTAACC CGAGCGTGGA

---

1751 GGACGCAGAT GGAAGACTTA AGGCAGCGGC AGAAGAAGAT GCAGGCAGCT  
 CCTGCGTCTA CCTTCTGAAT TCCGTCGCCG TCTTCTTCTA CGTCCGTCGA

---

1801 GAGTTGTTGT ATTCTGATAA GAGTCAGAGG TAACTCCCGT TGCGGTGCTG  
 CTCAACAACA TAAGACTATT CTCAGTCTCC ATTGAGGGCA ACGCCACGAC

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## pCMV-NS34A

## FIGURE 9 - Page 3

1851 TTAACGGTGG AGGGCAGTGT AGTCTGAGCA GTACTCGTTG CTGCCGCGCG  
AATTGCCACC TCCCGTCACA TCAGACTCGT CATGAGCAAC GACGGCGCGC

1901 CGCCACCAGA CATAATAGCT GACAGACTAA CAGACTGTTC CTTTCCATGG  
GCGGTGGTCT GTATTATCGA CTGTCTGATT GTCTGACAAG GAAAGGTACC

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1951 GTCTTTTCTG CAGTCACCGT CGTCGACCTA AGAATTCACC ATGGCGCCCA
CAGAAAAGAC GTCAGTGGCA GCAGCTGGAT TCTTAAGTGG TACCGCGGGT

+2

2001 I T A Y A Q Q T R G L L G C I I T
TCACGGCGTA CGCCCAGCAG ACAAGGGGCC TCCTAGGGTG CATAATCACC
AGTGCCGCAT GCGGGTCGTC TGTTCGCCG AGGATCCAC GTATTAGTGG

+2

2051 S L T G R D K N Q V E G E V Q I V
AGCCTAACTG GCGGGGACAA AAACCAAGTG GAGGGTGAGG TCCAGATTGT
TCGGATTGAC CGGCCCTGTT TTTGGTTCAC CTCCCACTCC AGGTCTAACA

+2

2101 S T A A Q T F L A T C I N G V C
GTCAACTGCT GCCCAAACCT TCCTGGCAAC GTGCATCAAT GGGGTGTGCT
CAGTTGACGA CGGGTTTGA AGGACCGTTG CACGTAGTTA CCCCACACGA

+2

2151 W T V Y H G A G T R T I A S P K G
GGACTGTCTA CCACGGGGCC GGAACGAGGA CCATCGCGTC ACCCAAGGGT
CCTGACAGAT GGTGCCCCG CTTGCTCCT GGTAGCGCAG TGGGTTCCTCA

-2

2201 P V I Q M Y T N V D Q D L V G W P
CCTGTCATCC AGATGTATAC CAATGTAGAC CAAGACCTTG TGGGCTGGCC
GGACAGTAGG TCTACATATG GTTACATCTG GTTCTGGAAC ACCCGACCGG

+2

2251 A S Q G T R S L T P C T C G S S
CGTTTCGCAA GGTACCCGCT CATTGACACC CTGCACTTGC GGCTCCTCGG
GCGAAGCGTT CCATGGGCGA GTAACGTGTG GACGTGAACG CCGAGGAGCC

+2

2301 D L Y L V T R H A D V I P V R R R
ACCTTTACCT GGTACAGAGG CACGCCGATG TCATTCCCGT GCGCCGGCGG
TGGAAATGGA CCAGTGCTCC GTGCGGCTAC AGTAAGGGCA CGCGGCCGCC

+2

2351 G D S R G S L L S P R P I S Y L K
GGTGATAGCA GGGGCAGCCT GCTGTGCGCC CGGCCCATTT CTTACTTGAA
CCACTATCGT CCCCCTCGGA CGACAGCGGG GCCGGGTAAA GGATGAACCT

+2

2401 G S S G G P L L C P A G H A V G
AGGCTCCTCG GGGGTTCGCG TGTGTGCCCC CGCGGGGCAC GCCGTGGGCA
TCCGAGGAGC CCCCAGGCG ACAACACGGG GCGCCCCGTG CGGCACCCGT

+2

2451 I F R A A V C T R G V A K A V D F
TATTTAGGGC CGCGGTGTGC ACCCGTGGAG TGGCTAAGGC GGTGGACTTT
ATAAATCCCG GCGCCACACG TGGGCACCTC ACCGATTCCG CCACCTGAAA

+2

2501 I P V E N L E T T M R S P V F T D
ATCCCTGTGG AGAACCTAGA GACAACCATG AGGTCCCCGG TGTTACGGGA
TAGGGACACC TCTTGATCT CTGTTGGTAC TCCAGGGGCC ACAAGTGCCT

CGCTTTCGCAA

+2 S G D V V V V A T D A L M T G Y T
 3201 GCGGCGATGT TGTCGTCGTG GCAACCGATG CCCTCATGAC CGGCTATACC
 CGCCGCTACA ACAGCAGCAC CGTTGGCTAC GGGAGTACTG GCCGATATGG

[illegible]

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FIGURE 9 - Page 5

+2 G D F D S V I D C N T C V T Q T V
3251 GCGACTTCG ACTCGGTGAT AGACTGCAAT ACGTGTGTCA CCCAGACAGT
CCGCTGAAGC TGAGCCACTA TCTGACGTTA TGCACACAGT GGGTCTGTCA

+2 D F S L D P T F T I E T I T L P
3301 CGATTTCAGC CTTGACCCTA CCTTCACCAT TGAGACAATC ACGCTCCCC
GCTAAAGTCG GAACTGGGAT GGAAGTGGTA ACTCTGTTAG TGCGAGGGGG

+2 Q D A V S R T Q R R G R T G R G K
3351 AAGATGCTGT CTCCCGCACT CAACGTCGGG GCAGGACTGG CAGGGGGAAG
TTCTACGACA GAGGGCGTGA GTTGACGCCC CGTCTGACC GTCCCCCTTC

+2 P G I Y R F V A P G E R P S G M F
3401 CCAGGCATCT ACAGATTTGT GGCACCGGGG GAGCGCCCCT CCGGCATGTT
GGTCCGTAGA TGTCTAAACA CCGTGGCCCC CTCGCGGGGA GGCCGTACAA

+2 D S S V L C E C Y D A G C A W Y
3451 CGACTCGTCC GTCCTCTGTG AGTGCTATGA CGCAGGCTGT GCTTGGTATG
GCTGAGCAGG CAGGAGACAC TCACGATACT GCGTCCGACA CGAACCATAC

+2 E L T P A E T T V R L R A Y M N T
3501 AGCTCACGCC CGCCGAGACT ACAGTTAGGC TACGAGCGTA CATGAACACC
TCGAGTGC GGCGCTCTGA TGTCAATCCG ATGCTCGCAT GTACTTGTGG

+2 P G L P V C Q D H L E F W E G V F
3551 CCGGGGCTTC CCGTGTGCCA GGACCATCTT GAATTTTGGG AGGGCGTCTT
GGCCCCGAAG GGCACACGGT CTTGGTAGAA CTTAAAACCC TCCCGCAGAA

+2 T G L T H I D A H F L S Q T K Q
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3601 TACAGGCCTC ACTCATATAG ATGCCCCACTT TCTATCCCAG ACAAAGCAGA  
ATGTCGGGAG TGAGTATATC TACGGGTGAA AGATAGGGTC TGTTCGTCT

+2 S G E N L P Y L V A Y Q A T V C A  
3651 GTGGGGAGAA CCTTCCTTAC CTGGTAGCGT ACCAAGCCAC CGTGTGCGCT  
CACCCCTCTT GGAAGGAATG GACCATCGCA TGGTTCGGTG GCACACGCGA

+2 R A Q A P P P S W D Q M W K C L I  
3701 AGGGCTCAAG CCCCTCCCC ATCGTGGGAC CAGATGTGGA AGTGTGTTGAT  
TCCCGAGTTC GGGGAGGGGG TAGCACCTG GTCTACACCT TCACAACTA

+2 R L K P T L H G P T P L L Y R L  
3751 TCGCCTCAAG CCCACCCTCC ATGGGCCAAC ACCCCTGCTA TACAGACTGG  
AGCGGAGTTC GGGTGGGAGG TACCGGTTG TGGGGACGAT ATGTCTGACC

+2 G A V Q N E I T L T H P V T K Y I  
3801 GCGCTGTTCA GAATGAAATC ACCCTGACGC ACCCAGTCAC CAAATACATC  
CGCGACAAGT CTTACTTTAG TGGGACTGCG TGGGTCAGTG GTTTATGTAG

+2 M T C M S A D L E V V T S T W V L  
3851 ATGACATGCA TGTGCGCCGA CCTGGAGGTC GTCACGAGCA CCTGGGTGCT  
TACTGTAGCT ACAGCCGGCT GGACCTCCAG CAGTGCTCGT GGACCCACGA

+2 V G G V L A A L A A Y C L S T G  
3901 CGTTGGCGGC GTCCTGGCTG CTTTGGCCGC GTATTGCCTG TCAACAGGCT  
GCAACCGCG CAGGACCGAC GAAACCGCG CATAACGGAC AGTTGTCCGA

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**FIGURE 9 - Page 6**

4801 CGGTAAGACA CGACTTATCG CCACTGGCAG CAGCCACTGG TAACAGGATT  
GCCATTCTGT GCTGAATAGC GGTGACCGTC GTCGGTGACC ATTGTCCTAA

## FIGURE 9 - Page 7

4851 AGCAGAGCGA GGTATGTAGG CGGTGCTACA GAGTTCTTGA AGTGGTGGCC  
TCGTCTCGCT CCATACATCC GCCACGATGT CTCAAGAACT TCACCACCGG

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4901 TAACTACGGC TACACTAGAA GGACAGTATT TGGTATCTGC GCTCTGCTGA  
ATTGATGCCG ATGTGATCTT CCTGTCATAA ACCATAGACG CGAGACGACT

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4951 AGCCAGTTAC CTTGCGAAAA AGAGTTGGTA GCTCTTGATC CGGCAAAACA  
TCGGTCAATG GAAGCCTTTT TCTCAACCAT CGAGAACTAG GCCGTTTGTT

---

5001 ACCACCGCTG GTAGCGGTGG TTTTTTTGTT TGCAAGCAGC AGATTACGCG  
TGGTGGCGAC CATCGCCACC AAAAAAACA ACGTTTCGTCG TCTAATGCGC

---

5051 CAGAAAAAAA GGATCTCAAG AAGATCCTTT GATCTTTTCT ACGGGGTCTG  
GTCTTTTTTT CCTAGAGTTC TTCTAGGAAA CTAGAAAAGA TGCCCCAGAC

---

5101 ACGCTCAGTG GAACGAAAAC TCACGTTAAG GGATTTTGGT CATGAGATTA  
TGCGAGTCAC CTTGCTTTTG AGTGCAATTC CCTAAAACCA GTACTCTAAT

---

5151 TCAAAAAGGA TCTTCACCTA GATCCTTTTA AATTAAAAAT GAAGTTTAA  
AGTTTTTCCT AGAAGTGGAT CTAGGAAAAT TTAATTTTTA CTTCAAAATT

---

5201 ATCAATCTAA AGTATATATG AGTAACTTG GTCTGACAGT TACCAATGCT  
TAGTTAGATT TCATATATAC TCATTGAAC CAGACTGTCA ATGGTTACGA

---

5251 TAATCAGTGA GGCACCTATC TCAGCGATCT GTCTATTTTCG TTCATCCATA  
ATTAGTCACT CCGTGGATAG AGTCGCTAGA CAGATAAAGC AAGTAGGTAT

---

5301 GTTGCCCTGAC TCCCCGTCGT GTAGATAACT ACGATACGGG AGGGCTTACC  
CAACGGACTG AGGGGCAGCA CATCTATTGA TGCTATGCCC TCCCGAATGG

---

5351 ATCTGCCCCC AGTGCTGCAA TGATACCGCG AGACCCACGC TCACCGGCTC  
TAGACCGGGG TCACGACGTT ACTATGGCGC TCTGGGTGCG AGTGCCGAG

---

5401 CAGATTTATC AGCAATAAAC CAGCCAGCCG GAAGGGCCGA GCGCAGAAGT  
GTCTAAATAG TCGTTATTG GTCGGTCGGC CTTCCCGGCT CGCGTCTTCA

---

5451 GGTCTGCAA CTTTATCCGC CTCCATCCAG TCTATTAATT GTTGCCGGGA  
CCAGGACGTT GAAATAGGCG GAGGTAGGTC AGATAATTAA CAACGGCCCT

---

5501 AGCTAGAGTA AGTAGTTCGC CAGTTAATAG TTTGCGCAAC GTTGTTGCCA  
TCGATCTCAT TCATCAAGCG GTCAATTATC AAACGCGTTG CAACAACGGT

---

5551 TTGCTACAGG CATCGTGGTG TCACGCTCGT CGTTTGGTAT GGCTTCATTC  
AACGATGTCC GTAGCACCAC AGTGCGAGCA GCAAACCATA CCGAAGTAAG

---

5601 AGCTCCGGTT CCCAACGATC AAGGCGAGTT ACATGATCCC CCATGTTGTG  
TCGAGGCCAA GGGTTGCTAG TTCCGCTCAA TGTACTAGGG GGTACAACAC

---

5651 CAAAAAGCG GTTAGCTCCT TCGGTCCTCC GATCGTTGTC AGAAGTAAGT  
GTTTTTTCGC CAATCGAGGA AGCCAGGAGG CTAGCAACAG TCTTCATTCA

---

5701 TGGCCGCGAGT GTTATCACTC ATGGTTATGG CAGCACTGCA TAATTCTCTT  
ACCGGCGTCA CAATAGTGAG TACCAATACC GTCGTGACGT ATTAAGAGAA

---

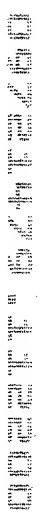
5751 ACTGTCATGC CATCCGTAAG ATGCTTTTCT GTGACTGGTG AGTACTCAAC  
TGACAGTACG GTAGGCATTC TACGAAAAGA CACTGACCAC TCATGAGTTG

---

**FIGURE 9 - Page 8**

5801	CAAGTCATTC GTTTCAGTAAG	TGAGAATAGT ACTCTTATCA	GTATGCGGCG CATACGCCGC	ACCGAGTTGC TGGCTCAACG	TCTTGCCCGG AGAACGGGCC
5851	CGTCAATACG GCAGTTATGC	GGATAATACC CCTATTATGG	GCGCCACATA CGCGGTGTAT	GCAGAACTTT CGTCTTGAAA	AAAAGTGCTC TTTTACAGAG
5901	ATCATTGGAA TAGTAACCTT	AACGTTCTTC TTGCAAGAAG	GGGGCGAAAA CCCCGCTTTT	CTCTCAAGGA GAGAGTTCCCT	TCTTACCGCT AGAATGGCGA
5951	GTTGAGATCC CAACTCTAGG	AGTTCGATGT TCAAGCTACA	AACCCACTCG TTGGGTGAGC	TGCACCCAAC ACGTGGGTTG	TGATCTTCAG ACTAGAAGTC
6001	CATCTTTTAC GTAGAAAATG	TTTCACCAGC AAAGTGGTCG	GTTTCTGGGT CAAAGACCCA	GAGCAAAAAC CTCGTTTTTG	AGGAAGGCAA TCCTTCCGTT
6051	AATGCCGCAA TTACGGCGTT	AAAAGGGAAT TTTTCCCTTA	AAGGGCGACA TTCCCGCTGT	CGGAAATGTT GCCTTTACAA	GAATACTCAT CTTATGAGTA
6101	ACTCTTCCCT TGAGAAGGAA	TTTCAATATT AAAGTTATAA	ATTGAAGCAT TAACTTCGTA	TTATCAGGGT AATAGTCCCA	TATTGTCTCA ATAACAGAGT
6151	TGAGCGGATA ACTCGCCTAT	CATATTTGAA GTATAAACTT	TGTATTTAGA ACATAAATCT	AAAATAAACA TTTTATTTGT	AATAGGGGTT TTATCCCCAA
6201	CCGCGCACAT GGCGCGTGTA	TTCCCCGAAA AAGGGGCTTT	AGTGCCACCT TCACGGTGGA	GACGTCTAAG CTGCAGATTG	AAACCATTAT TTTGGAATAA
6251	TATCATGACA ATAGTACTGT	TTAACCTATA AATTGGATAT	AAAATAGGCG TTTTATCCGC	TATCACGAGG ATAGTGCTCC	CCCTTTTCGT GGGAAAGCAG



**FIGURE 10**

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429	2430	2431	2432	2433	2434	2435	2436	2437	2438	2439	2440	2441	2442	2
--	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	---

CysAsnThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGlu

[illegible]

662 TGCAATACGTGTGTACCCAGACAGTCGATTTTCAGCCTTGACCCTACCTTCACCATTGAG  
ACGTTATGCACACAGTGGGTCTGTCTCAGCTAAAGTCGGAACCTGGGATGGAAGTGGTAACTC

722 ThrIleThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArg  
ACAATCACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGG  
TGTTAGTGCAGGGGGTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCTTGACCGTCC

782 GlyLysProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAsp  
GGGAAGCCAGGCATCTACAGATTTGTGGCACCGGGGAGCGCCCCCTCCGGCATGTTTCGAC  
CCCTTCGGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCGGTACAAGCTG

822 BGLI, 839 DRD1,

842 SerSerValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAla  
TCGTCCGTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCGCC  
AGCAGGCAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGG

887 SACI,

902 GluThrThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAsp  
GAGACTACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGAC  
CTCTGATGTCAATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCTTG

937 SMAI XMAI,

962 HisLeuGluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeu  
CATCTTGAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCACTTTCTA  
GTAGAACTTAAACCCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGAT

991 STUI,

1022 SerGlnThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrVal  
TCCCAGACAAAGCAGAGTGGGGAGAACCTTCCCTTACCTGGTAGCGTACCAAGCCACCGTG  
AGGGTCTGTTTCGTCTCACCCCTCTTGGGAAGGAATGGACCATCGCATGGTTCGGTGGCAC

1075 DRA3,

1082 CysAlaArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArg  
TGCGCTAGGGCTCAAGCCCTCCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTTCG  
ACGCGATCCCAGTTCGGGGAGGGGGTAGCACCTGGTCTACACCTTCACAACTAAGCG

1142 LeuLysProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsn  
CTCAAGCCCACCCTCCATGGGCCAACACCCCTGCTATACAGACTGGGCGCTGTTGAGAAT  
GAGTTCGGGTGGGACTACCCGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTA

1156 NCOI,

1202 GluIleThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeu  
GAAATCACCTGACGCACCCAGTACCAAATACATCATGACATGCATGTGGCCGACCTG  
CTTTAGTGGGACTGCGTGGGTGAGTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGAC

1236 BSPH1, 1240 DRD1, 1243 AVA3, 1251 EAG1 XMA3, 1256 DRD1,

1262 GluValValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyr  
GAGGTCGTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCTGGCTGCTTTGGCCGCGTAT  
CTCCAGCAGTGCTCGTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATA

# FIGURE 11 - Page 3

CysLeuSerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAla  
 1322 TGCCTGTCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCCGGGAAGCCGGCA  
 ACGGACAGTTGTCCGACGCACCAGTATCACCCGTCAGCAGAACAGGCCCTTCGGCCGT  
 ^  
 1375 NAEI,  
 IleIleProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGln  
 1382 ATCATACCTGACAGGGAAGTCCTCTACCGAGAGTTTCGATGAGATGGAAGAGTGCTCTCAG  
 TAGTATGGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCACGAGAGTC  
 ^  
 1391 DRD1,  
 HisLeuProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeu  
 1442 CACTTACCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTC  
 GTGAATGGCATGTAGCTCGTTCCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAG  
 GlyLeuLeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsn  
 1502 GGCCTCCTGCAGACCGCGTCCCGTCAGGCAGAGTTATCGCCCTGCTGTCCAGACCAAC  
 CCGGAGGACGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTG  
 ^ ^  
 1508 PSTI, 1513 TTH3I,  
 TrpGlnLysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGln  
 1562 TGGCAAAACTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAA  
 ACCGTTTTTGTAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCATGTT  
 ^ ^  
 1571 XHOI, 1592 NDEI,  
 TyrLeuAlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPhe  
 1622 TACTTGGCGGGCTTGTCAACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTT  
 ATGAACCGCCCGAACAGTTGCGACGGACCATTGGGGCGGTAACGAAGTAACACCGAAAA  
 ^  
 1649 BSTE2,  
 ThrAlaAlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGly  
 1682 ACAGCTGCTGTCAACAGCCCACTAACCACTAGCCAAACCCCTCCTCTTCAACATATTGGGG  
 TGTGACGACAGTGGTCCGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCC  
 ^  
 1683 ALWN1 PVU2,  
 GlyTrpValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGly  
 1742 GGGTGGGTGGCTGCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGC  
 CCCACCCACCGACGGGTCGAGCGGCGGGGGCCACGGCGATGACGGAAACACCCGCGACCG  
 ^  
 1800 ESP1,  
 LeuAlaGlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAla  
 1802 TTAGCTGGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCCTCATAGACATCCTTGCA  
 AATCGACCGCGGCGGTAGCCGTCAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGT  
 ^  
 1808 KAS1 NARI,  
 GlyTyrGlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluVal  
 1862 GGGTATGGCGCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTC  
 CCCATACCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAG  
 ^ ^

00221524260

[illegible]

ProSerThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuVal  
1922 CCCTCCACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTA  
GGGAGGTGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCAT  
1934 TTH3I,  
ValGlyValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaVal  
1982 GTCGGCGTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCCGGGCGAGGGGGCAGTG  
CAGCCGCACCAGACAGTCGTTATGACGCGGGCGTGCAACCGGGCCCCGCTCCCCCGTCAC  
2010 NAEI, 2023 SMAI XMAI,  
GlnTrpMetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHis  
2042 CAGTGGATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTTCCCCCACGCAC  
GTCACCTACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGTGCGTG  
2073 SMAI XMAI, 2099 DRA3,  
TyrValProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrVal  
2102 TACGTGCCGGAGAGCGATGCAGCTGCCCCGCTCACTGCCATACTCAGCAGCCTCACTGTA  
ATGCACGGCCTCTCGCTACGTCGACGGGCGCAGTGACGGTATGAGTCGTGCGAGTGACAT  
2121 PVU2,  
ThrGlnLeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSer  
2162 ACCCAGCTCCTGAGGCGACTGCACCAGTGGATAAGCTCGGAGTGTACCACTCCATGCTCC  
TGGGTGCGAGGACTCCGCTGACGTGGTCACCTATTTCGAGCCTCACATGGTGAGGTACGAGG  
2165 ALWN1, 2170 MST2,  
GlySerTrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThr  
2222 GGTTCCTGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACC  
CCAAGGACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACTCGCTGAAATTCTGG  
2226 ECON1,  
TrpLeuLysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArg  
2282 TGGCTAAAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCTTTGTGTCTGCCAGCGC  
ACCGATTTTCGATTGAGTACGGTGTCGACGGACCCTAGGGGAAACACAGGACGGTTCGGC  
2291 ESP1, 2306 PVU2, 2316 BAMHI,  
GlyTyrLysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAla  
2342 GGGTATAAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGTGCCACTGTGGAGCT  
CCCATATTCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGA  
2402 GluIleThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArg  
GAGATCACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCTAGGACCTGCAGG  
CTCTAGTGACCTGTACAGTTTTTTGCCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCC  
2431 BSAB1, 2447 AVR2, 2454 SSE83871, 2455 PSTI,  
AsnMetTrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeu  
2462 AACATGTGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCCGTACCCCCCTT  
TTGTACACCTCACCTGGAAGGGGTAAATTACGGATGTGGTGCCCGGGGACATGGGGGGAA



# FIGURE 11 - Page 6

IleLeuArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyr  
 3122 ATCCTGCGGAAGTCTCGGAGATTCGCCCAGGCCCTGCCCGTTTGGGCGCGGCCGACTAT  
 TAGGACGCCCTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGCTGATA  
 3149 ALWN1, 3170 EAG1 XMA3,  
 AsnProProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGly  
 3182 AACCCCCCGCTAGTGGAGACGTGGAAAAAGCCCGACTACGAACCACCTGTGGTCCATGGC  
 TTGGGGGGCGATCACCTCTGCACCTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCG  
 3223 HGIE2, 3235 NCOI,  
 CysProLeuProProProLysSerProProValProProProArgLysLysArgThrVal  
 3242 TGCCCGCTTCCACCTCCAAAGTCCCCCTCCTGTGCCTCCGCTCGGAAGAAGCGGACGGTG  
 ACGGGCGAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCTGCCAC  
 ValLeuThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGly  
 3302 GTCCTCACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGC  
 CAGGAGTGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCG  
 3338 SACI, 3352 HIND3,  
 SerSerSerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaPro  
 3362 AGCTCCTCAACTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCGCCCT  
 TCGAGGAGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGA  
 SerGlyCysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGly  
 3422 TCTGGCTGCCCCCGGACTCCGACGTGAGTCCTATTCTCCATGCCCCCTGGAGGGG  
 AGACCGACGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGACCTCCCC  
 3443 EAM11051,  
 GluProGlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsn  
 3482 GAGCCTGGGGATCCGGATCTTAGCGACGGGTATGGTCAACGGTCAGTAGTGAGCCAAC  
 CTCGGACCCCTAGGCCTAGAATCGCTGCCCAGTACCAGTTGCCAGTCATCACTCCGGTTG  
 3490 BAMHI, 3491 BSAB1, 3493 BSPE1,  
 AlaGluAspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrPro  
 3542 GCGGAGGATGTCTGTGCTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCG  
 CGCCTCCTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGC  
 3595 DRA3,  
 CysAlaAlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHis  
 3602 TGCGCCGCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTAC  
 ACGCGGCGCCTTCTTGTCTTTGACGGGTAGTTACGTGATTTCGTTGAGCAACGATGCAGTG  
 3606 SAC2, 3617 ALWN1, 3661 PFLM1,  
 HisAsnLeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThr  
 3662 CACAATTTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAGAAAGTCACA  
 GTGTTAAACCACATAAGGTGGTGGAGTGCGTCACGAACGGTTTCCGTCTTCTTTAGTGT  
 3687 DRA3,  
 PheAspArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAla

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ACGCCGATAGCTCCACGGCGCGCTCGCCGATGACTGTTGATCGACACCATTTGTGGGAG

4442 ThrCysTyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMet  
ACTTGCTACATCAAGGCCCGGGCAGCCTGTCGAGCCGAGGGCTCCAGGACTGCACCATG  
TGAACGATGTAGTTCGGGGCCCGTCGGACAGCTCGGCGTCCCGAGGTCCTGACGTGGTAC  
4458 SMAI XMAI,

4502 LeuValCysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAla  
CTCGTGTGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGGTCCAGGAGGACGCG  
GAGCACACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCTCTCTGCGC  
4514 DRD1, 4517 TTH3I,

4562 AlaSerLeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspPro  
GCGAGCCTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCCTGGGGACCCC  
CGCTCGGACTCTCGGAAGTGCCTCCGATACTGGTCCATGAGGCGGGGGGACCCCTGGGG

4622 ProGlnProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAla  
CCACAACCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTCTAGTCGCC  
GGTGTGGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGG  
4643 SACI,

4682 HisAspGlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAla  
CACGACGGCGCTGGAAAGAGGGTCTACTACCTCACCCGTGACCTACAACCCCCCTCGCG  
GTGCTGCCGCGACCTTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGGAGCGC  
4737 NRUI,

4742 ArgAlaAlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIle  
AGAGCTGCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATC  
TCTCGACGCACCCTCTGTCGTCTGTGTGAGGTCAAGTAAAGACCGATCCGTTGTATTAG

4802 MetPheAlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeu  
ATGTTTGGCCCCACACTGTGGGCGAGGATGATACTGATGACCCATTCTTTAGCGTCTCT  
TACAAACGGGGGTGTGACACCCGCTCCTACTATGACTACTGGGTAAAGAAATCGCAGGAA  
4812 PFLM1, 4813 DRA3,

4862 IleAlaArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSer  
ATAGCCAGGGACAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCC  
TATCGGTCCCTGGTCAACTTGTCCGGGAGCTAACGCTCTAGATGCCCCGACGATGAGG  
4899 BGL2,

4922 IleGluProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSer  
ATAGAACCCTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCA  
TATCTTGGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTCGCGTAAAGT  
4960 NCOI,

4982 LeuHisSerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGly  
CTCCACAGTTACTCTCAGGTGAAATCAATAGGGTGGCCGATGCCTCAGAAAACCTTGGG  
GAGGTGTCAATGAGAGGTCCACTTTAGTTATCCACCGCGTACGGAGTCTTTTGAACCC  
5021 SPHI, 5041 KPNI,

# FIGURE 11 - Page 9

ValProProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAla  
 5042 GTACCGCCCTTGCGAGCTTGGAGACACCGGGCCCGGAGCGTCCGCGCTAGGCTTCTGGCC  
 CATGGCGGGAACGCTCGAACCTCTGTGGCCCGGGCCTCGCAGGCGCGATCCGAAGACCGG  
 ^ ^  
 5070 APAI, 5097 BALI,  
 ArgGlyGlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLys  
 5102 AGAGGAGGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAG  
 TCTCCTCCGTCCCGACGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTTGTTC  
 ^  
 5119 NDEI,  
 LeuLysLeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAla  
 5162 CTCAAACCTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTACGGCT  
 GAGTTTGAGTGAGGTTATCGCCGGCGACCGGTCGACCTGAACAGGCCGACCAAGTGCCGA  
 ^ ^ ^  
 5180 NOTI, 5181 EAG1 XMA3, 5188 BALI, 5192 PVU2,  
 GlyTyrSerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrp  
 5222 GGCTACAGCGGGGAGACATTTATCACAGCGTGTCTCATGCCCGGCCCGCTGGATCTGG  
 CCGATGTCGCCCCCTCTGTAAATAGTGTGCGCACAGAGTACGGGCCGGGGCGACCTAGACC  
 ^  
 5246 DRA3,  
 PheCysLeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgOP  
 5282 TTTTGCCTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCAACCGATGAAGG  
 AAAACGGATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTTGGCTACTTCC  
 ^ ^  
 5301 PSTI, 5331 HGIE2,  
 TTGGGGTAAACACTCCGGCCTAAAAAAAAAAAAAATCTAGAACCCGAGTCGAC  
 5342 AACCCCATTTGTGAGGCCGATTNTTTTTTTTTTTTAGATCTTGGGCTCAGCTG  
 ^ ^  
 5378 XBAI, 5390 SALI,

00227-64760

FIGURE 12

~~No~~  
SB  
std

PAS  
C

C.1 C.2

KD<sub>cr</sub>

250

-

98

-

64

-

50

-

36

-

30

-

16

-

6

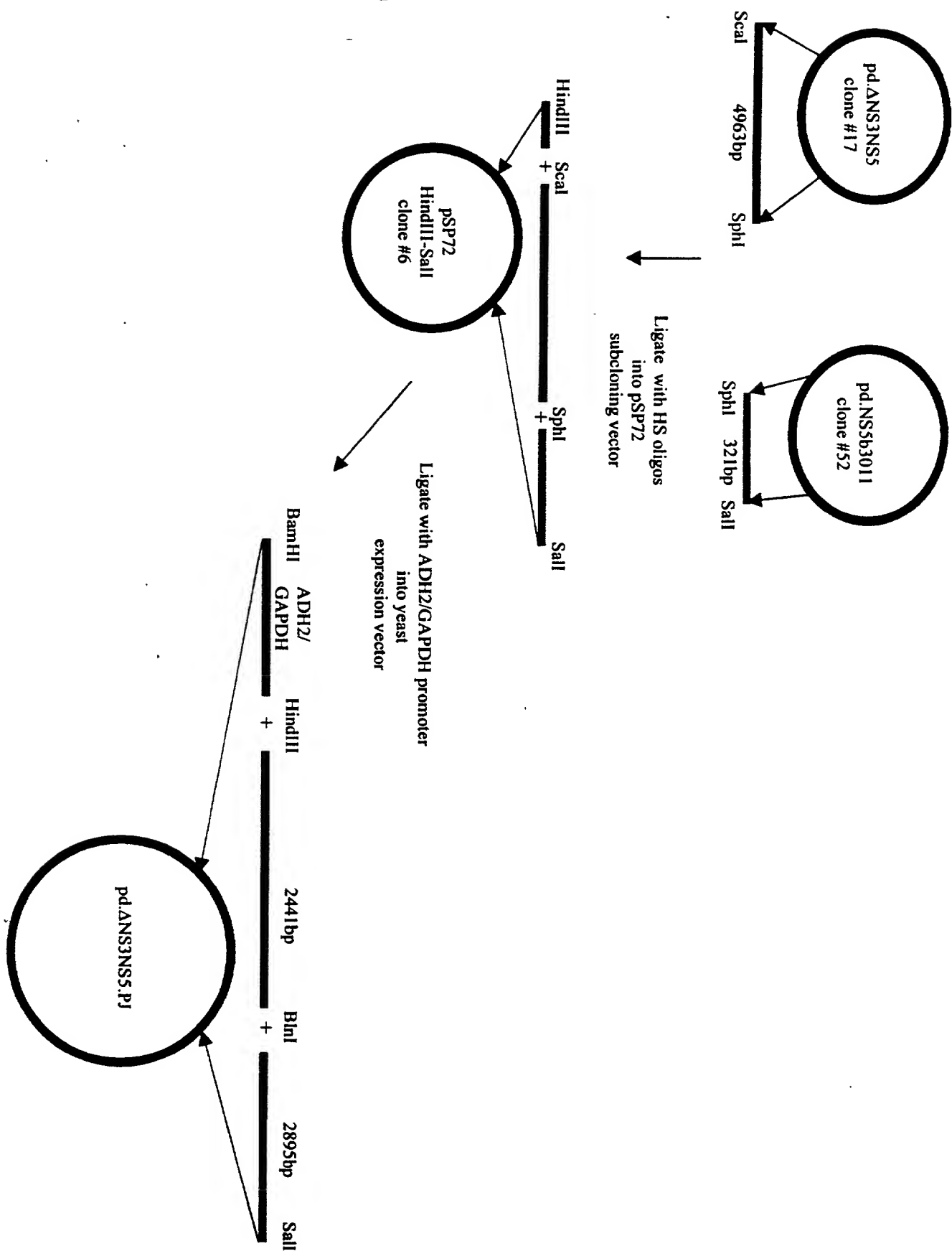
-

4

-

002211 02412260

FIGURE 13



[illegible]

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn  
2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC  
TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG  
^ ^ ^  
1 HIND3, 24 NDEI, 52 SCAI,  
  
ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp  
62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT  
GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA  
^  
116 CLAI,  
  
ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr  
122 CCTAACATCAGGACCGGGGTGAGAACAAATTACCACTGGCAGCCCCATCACGTACTCCACC  
GGATTGTAGTCTTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATGAGGTGG  
  
TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys  
182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT  
ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGCAATACTGTATTATTAAACA  
  
AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln  
242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA  
CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAC TGTT  
  
AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal  
302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC  
CGTCTCTGACGCCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCAG  
^  
303 ALWN1,  
  
ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe  
362 ACTGTGCCCCATCCCAACATCGAGGAGGTGCTCTGTCCACCACCGGAGAGATCCCTTTT  
TGACACGGGGTAGGGTTGTAGCTCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA  
  
TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis  
422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGGAGACATCTCATCTTCTGTCAT  
ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA  
  
SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal  
482 TCAAAGAAGAAGTGCGACGAACTCGCCGCAAAGCTGGTTCGATTGGGCATCAATGCCGTG  
AGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC  
  
AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal  
542 GCCTACTACCGCGGTCTTGACGTGTCCGTCATCCCGACCAGCGGCGATGTTGTCGTCGTG  
CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTTCGCCGCTACAACAGCAGCAC  
^ ^  
550 SAC2, 560 DRD1,  
  
AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn  
602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT  
CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA  
^  
615 BSPH1,  
  
ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle

662 ACGTGTGTCACCCAGACAGTCGATTTTCAGCCTTGACCCTACCTTCACCATTGAGACAATC  
 TGCACACAGTGGGTCTGTCTAGCTAAAGTCGGAAGTGGGATGGAAGTGGTAACTCTGTTAG  
 ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys  
 722 ACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGGAAG  
 TCGAGGGGGTTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCCTGACCGTCCCCCTTC  
 ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer  
 782 CCAGGCATCTACAGATTTGTGGCACCAGGGGAGCGCCCTCCGGCATGTTGACTCGTCC  
 GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG  
 816 BGLI, 833 DRD1,  
 ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr  
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCCGAGACT  
 CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGGCTCTGA  
 881 SACI,  
 ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu  
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT  
 TGTCATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCTCTGGTAGAA  
 931 SMAI XMAI,  
 GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln  
 962 GAATTTTGGGAGGGCGTCTTTACAGGCTCACTCATATAGATGCCACTTTCTATCCCAG  
 CTTAAACCCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC  
 985 STUI,  
 ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla  
 1022 ACAAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT  
 TGTTTCGTCTCACCCCTCTTGAAGGAATGGACCATCGCATGGTTTCGGTGGCACACGCGA  
 1069 DRA3,  
 ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys  
 1082 AGGGCTCAAGCCCCTCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTGCGCTCAAG  
 TCCCGAGTTCGGGGAGGGGGTAGCACCCCTGGTCTACACCTTCACAACTAAGCGGAGTTC  
 ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle  
 1142 CCCACCCTCCATGGGCCAACACCCCTGCTATACAGACTGGGCGCTGTTTCAAGATGAAATC  
 GGGTGGGAGGTACCCGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG  
 1150 NCOI,  
 ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal  
 1202 ACCCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTGGCCGACCTGGAGGTC  
 TGGGACTGCGTGGGTGAGTGGTTTATGTACTGTACGTACAGCCGGCTGGACCTCCAG  
 1230 BSPH1, 1234 DRD1, 1237 AVA3, 1245 EAG1 XMA3, 1250 DRD1,  
 ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu  
 1262 GTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCTGGCTGCTTTGGCCGCGTATTGCCTG  
 CAGTGCTCGTGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATAACGGAC

SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle  
 1322 TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCCGGGAAGCCGGCAATCATA  
 AGTTGTCCGACGCACCAGTATCACCCGTCCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT  
 ^  
 1369 NAEI,  
 ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu  
 1382 CCTGACAGGGAAGTCTCTACCGAGAGTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA  
 GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCACGAGAGTCGTGAAT  
 ^  
 1385 DRD1,  
 ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu  
 1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAGCAGAAGGCCCTCGGCCTC  
 GGCATGTAGCTCGTTCCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAGCCGGAG  
 LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln  
 1502 CTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCCCTGTGTCCAGACCAACTGGCAA  
 GACGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTGACCGTT  
 ^ ^  
 1502 PSTI, 1507 TTH3I,  
 LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu  
 1562 AAACTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG  
 TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCTATGTTATGAAC  
 ^ ^  
 1565 XHOI, 1586 NDEI,  
 AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla  
 1622 GCGGGCTTGTCACCGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT  
 CGCCCGAACAGTTGCGACGGACCATTGGGGCGGTAACGAAGTAACTACCGAAAATGTCGA  
 ^ ^  
 1643 BSTE2, 1677 ALWN1 PVU2,  
 AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp  
 1682 GCTGTACACGACCCACTAACCCTAGCCAAACCCTCCTCTTCAACATATTGGGGGGGTGG  
 CGACAGTGGTCCGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC  
 ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla  
 1742 GTGGCTGCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT  
 CACCGACGGGTGAGCGGGCGGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA  
 ^  
 1794 ESP1,  
 GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr  
 1802 GGCGCCGCCATCGGCAGTGTTGGACTGGGGAAGGTCCTCATAGACATCCTTGACGGGTAT  
 CCGCGGCGGTAGCCGTCAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCATA  
 ^  
 1802 KAS1 NARI,  
 GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer  
 1862 GGCGCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCTCC  
 CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG  
 ^ ^  
 1878 SACI, 1899 BSPH1,

00231T"54T5450

# FIGURE 14 - Page 4

ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly  
 1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCCTAGTCGGC  
 TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG  
 ^  
 1928 TTH3I,  
 ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp  
 1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCGGGCGAGGGGGCAGTGCAGTGG  
 CACCAGACACGTCGTTATGACGCGGCCGTGCAACCGGGCCCGCTCCCCCGTCACGTCACC  
 ^ ^  
 2004 NAEI, 2017 SMAI XMAI,  
 MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal  
 2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTCCCCACGCACTACGTCG  
 TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGGTGCCTGATGCAC  
 ^ ^  
 2067 SMAI XMAI, 2093 DRA3,  
 ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln  
 2102 CCGGAGAGCGATGCAGCTGCCCGCTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG  
 GGCCTCTCGCTACGTCGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTC  
 ^ ^  
 2115 PVU2, 2159 ALWN1,  
 LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer  
 2162 CTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTAACCTCCATGCTCCGGTTCC  
 GAGGACTCCGCTGACGTGGTCACCTATTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG  
 ^ ^  
 2164 MST2, 2220 ECON1,  
 TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu  
 2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA  
 ACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT  
 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr  
 2282 AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCCTTTGTGTCCTGCCAGCGCGGGTAT  
 TTTGATTGAGTACGGTGTGACGGACCCTAGGGGAAACACAGGACGGTTCGCGCCCATG  
 ^ ^ ^  
 2285 ESP1, 2300 PVU2, 2310 BAMHI,  
 LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle  
 2342 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC  
 TTCCCCCAGACCGCTCCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG  
 ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet  
 2402 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCCTAGGACCTGCAGGAACATG  
 TGACCTGTACAGTTTTTGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCCTTGTAC  
 ^ ^ ^  
 2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,  
 TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla  
 2462 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCCCTGTACCCCCCTTCTGCG  
 ACCTCACCTGGAAGGGGTAATTACGGATGTGGTGCCCGGGGACATGGGGGGAAGGACGC  
 ^ ^  
 2480 ASE1, 2497 APAI,  
 ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln

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Figure 1 consists of 12 sub-graphs labeled (a) through (l). Each graph plots a different parameter on the y-axis against the number of fish (N) on the x-axis, which ranges from 0 to 10. The parameters are: (a) Oxygen consumption, (b) Oxygen consumption, (c) Oxygen consumption, (d) Oxygen consumption, (e) Oxygen consumption, (f) Oxygen consumption, (g) Oxygen consumption, (h) Oxygen consumption, (i) Oxygen consumption, (j) Oxygen consumption, (k) Oxygen consumption, and (l) Oxygen consumption. The graphs show various trends, including linear increases, decreases, and non-linear relationships.

ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla  
3722 AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGCG  
TCTGACGTTCAAGACCTGTCGGTAATGGTCCTGCATGAGTTCCTCCAATTTTCGTCGCCGC

3782 SerLysValLysAlaAsnLeuSerValGluGluAlaCysSerLeuThrProProHis  
TCAAAAGTGAAGGCTAAGTTGCTATCCGTAGAGGAAGCTTGCAGCCTGACGCCCCACAC  
AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTCGGACTGCGGGGGTGTG  
3816 HIND3,  
3842 SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla  
TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAGACGTCCGTTGCCATGCCAGAAAGGCC  
AGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCTTTCCGG  
3875 AAT2, 3890 BGLI,  
3902 ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp  
GTAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAACACCAATAGAC  
CATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGTTATCTG  
3962 ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys  
ACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTTGCAGCCTGAGAAGGGGGTTCGTAAG  
TGATGGTAGTACCGATTCTTGCTCCAAAGACGCAAGTCGGACTCTTCCCCCAGCATTC  
4022 ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu  
CCAGCTCGTCTCATCGTGTTCCTCCGATCTGGGCGTGCAGCGTGTGCGAAAAGATGGCTTTG  
GGTCGAGCAGAGTAGCACAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTACCGAAAC  
4082 TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr  
TACGACGTGGTTACAAAGCTCCCCTTGGCCGTGATGGGAAGCTCCTACGGATTCCAATAC  
ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAGGTTATG  
4142 SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet  
TCACCAGGACAGCGGGTTGAATTCCTCGTGCAAGCGTGAAGTCCAAGAAAACCCCAATG  
AGTGGTCTCTGCGCCCACTTAAGGAGCACGTTGCGACCTTCAGGTTCTTTTGGGTTAC  
4160 ECORI,  
4202 GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr  
GGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG  
CCCAAGAGCATACTATGGGCGACGAAACTGAGGTGTGAGTACTCTCGCTGTAGGCATGC  
4229 DRD1, 4236 ALWN1,  
4262 GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer  
GAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCCAAGCCCGCTGGCCATCAAGTCC  
CTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTGCGGCGCACCGGTAGTTCAGG  
4301 BGLI, 4308 BALI,  
4322 LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly  
CTCACCAGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAACTGCGGC  
GAGTGGCTCTCCGAAATACAACCCCGGGGAGAATGGTTAAGTTCCTCCCTCTTGACGCCG  
4345 APAI,  
4382 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys  
TATCGCAGGTGCCGCGCGAGCGCGTACTGACAACTAGCTGTGGTAACACCCCTCACTTGC  
ATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTGTGGGAGTGAACG

2

# FIGURE 14 - Page 9

5042 CCCTTGGCGAGCTTGGAGACACCGGGCCCGGAGCGTCCGCGCTAGGCTTCTGCCCAGAGGA  
 GGGAACGCTCGAACCTCTGTGGCCCGGGCCTCGCAGGCGCGATCCGAAGACCGGTCTCTCT  
 ^ ^

5064 APAI, 5091 BALI,

GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys  
 5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAAA  
 CCGTCCCGACGGTATACACCGTTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT  
 ^

5113 NDEI,

LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr  
 5162 CTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTCACGGCTGGCTAC  
 GAGTGAGGTTATCGCCGGCGACCGGTTCGACCTGAACAGGCCGACCAAGTGCCGACCGATG  
 ^ ^ ^ ^

5174 NOTI, 5175 EAG1 XMA3, 5182 BALI, 5186 PVU2,

SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys  
 5222 AGCGGGGAGACATTTATCACAGCGTGTCTCATGCCCGGGCCCGCTGGATCTGGTTTTGC  
 TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCCGGGGCGACCTAGACCAAACG  
 ^

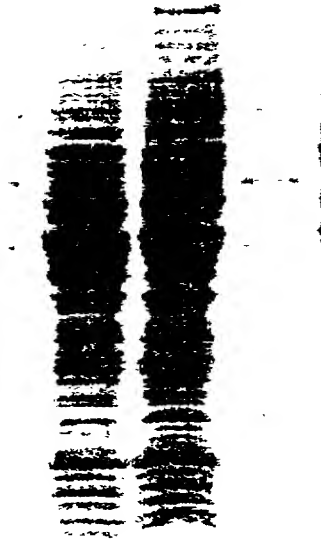
5240 DRA3,

LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgOP  
 5282 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCAACCGATGAATAGTCGAC  
 GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTACTTATCAGCTG  
 ^ ^

5295 PSTI, 5336 SALI,

00221164160

**FIGURE 15**



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FIGURE 16 - Page 1

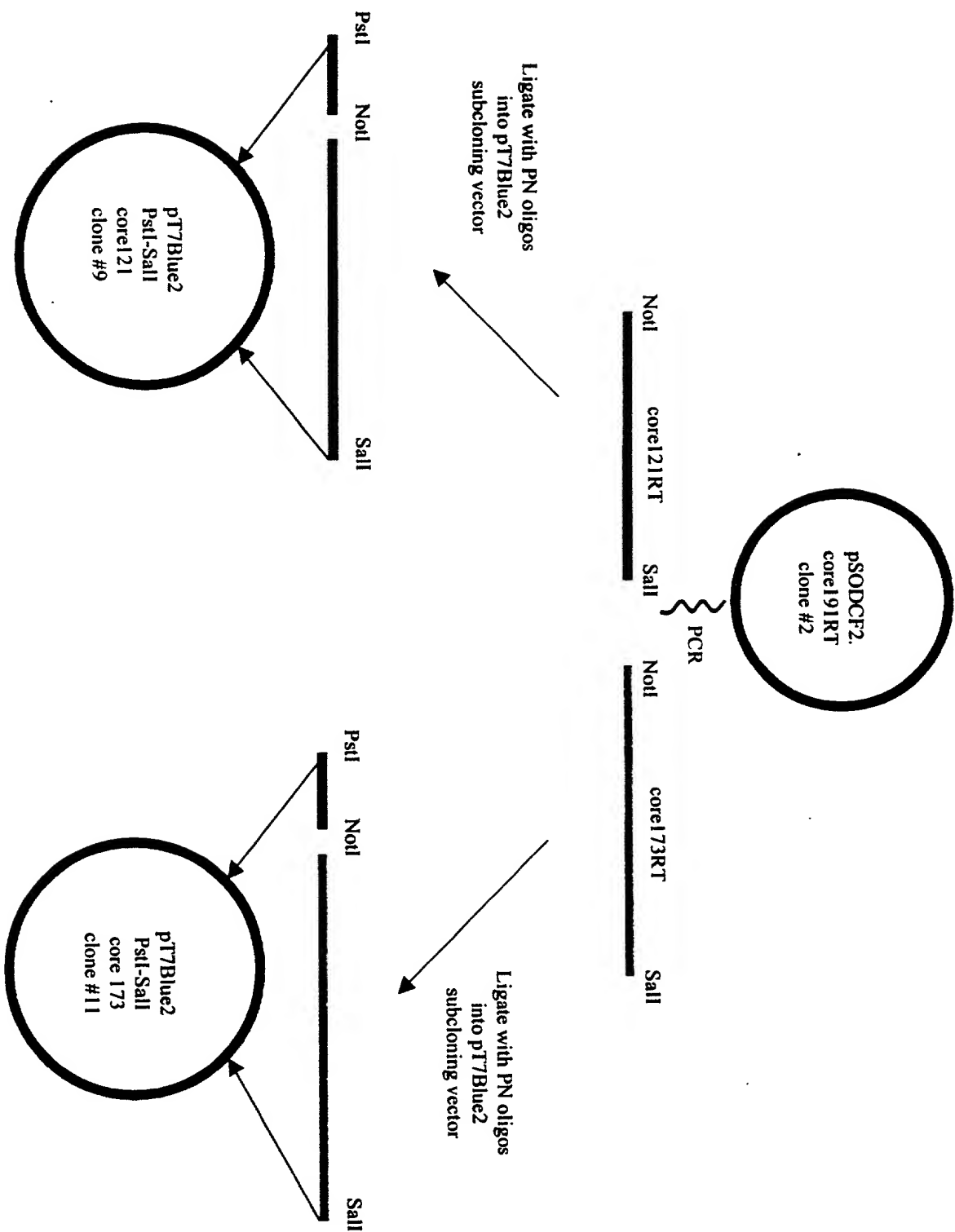
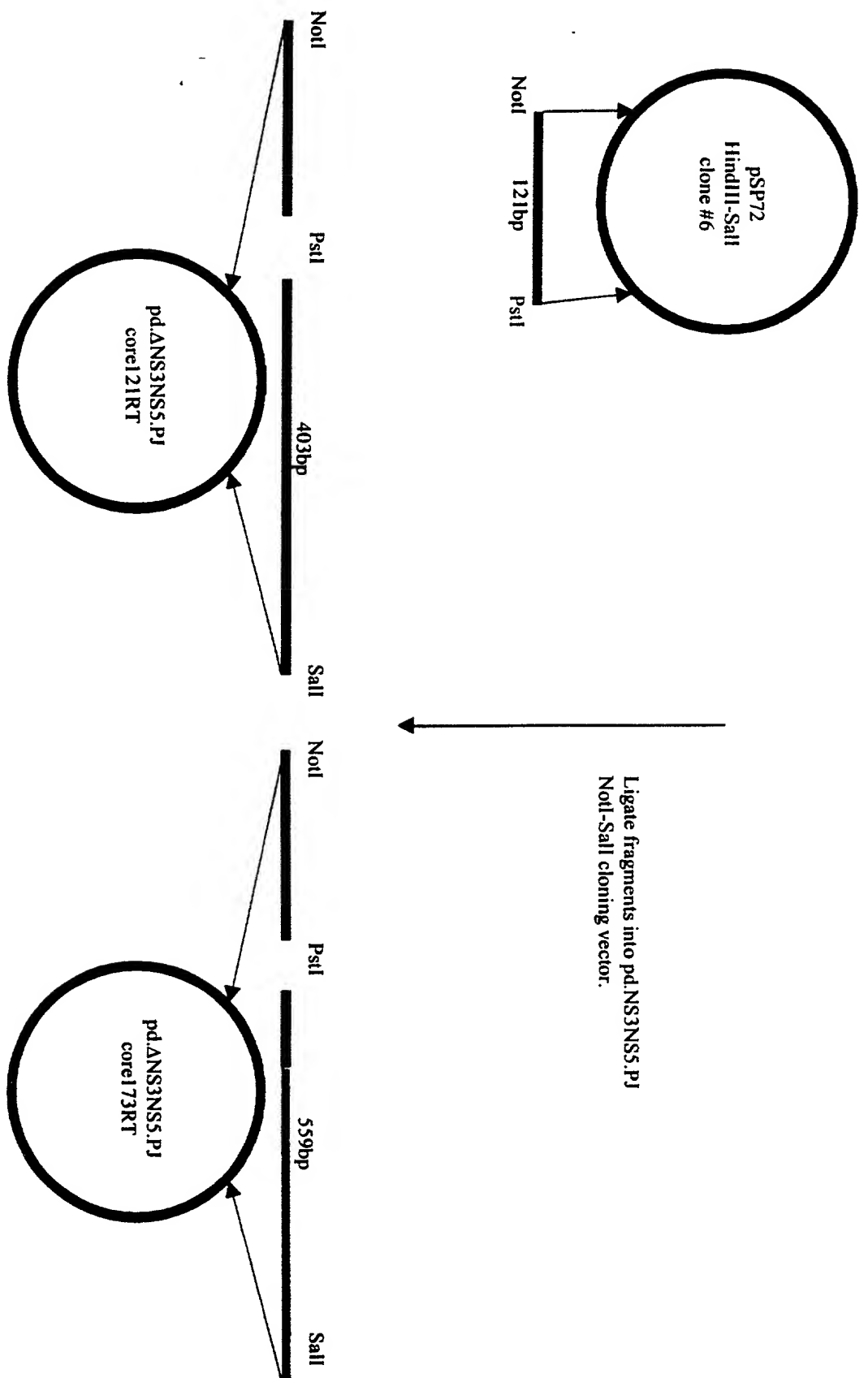


FIGURE 16 - Pa



Ligate fragments into pd,ANS3NSS5,PJ  
NotI-Sall cloning vector.



# FIGURE 17 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn  
 2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC  
 TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG  
 ^ ^ ^  
 1 HIND3, 24 NDEI, 52 SCAI,  
 ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp  
 62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT  
 GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA  
 ^  
 116 CLAI,  
 ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr  
 122 CCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCACGTACTCCACC  
 GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATGAGGTGG  
 TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys  
 182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT  
 ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGCAATACTGTATTATTAAACA  
 AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln  
 242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA  
 CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAACCTGTT  
 AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal  
 302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC  
 CGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCAG  
 ^  
 303 ALWN1,  
 ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe  
 362 ACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACGGAGAGATCCCTTTT  
 TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA  
 TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis  
 422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTGAT  
 ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA

00224460

[illegible]

SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal  
 482 TCAAAGAAGAAGTGCACGAACTCGCCGCAAAGCTGGTCGCATTGGGCATCAATGCCGTG  
 AGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC  
 AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal  
 542 GCCTACTACCGCGGTCTTGACGTGTCCGTCATCCCACCAGCGCGCATGTTGTGTCGTCGTG  
 CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAGCAGCAC  
 550 SAC2, 560 DRD1,  
 AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn  
 602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT  
 CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA  
 615 BSPH1,  
 ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle  
 662 ACGTGTGTACCCAGACAGTCGATTTACGCCCTTGACCTACCTTCACCATTGAGACAATC  
 TGCACACAGTGGGTCTGTCTCAGCTAAAGTCGGAAGTGGGATGGAAGTGGTAACCTCTGTTAG  
 ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys  
 722 ACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGAAG  
 TGCGAGGGGGTTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCTGACCGTCCCCCTTC  
 ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer  
 782 CCAGGCATCTACAGATTGTGGCACCGGGGAGCGCCCCCTCCGGCATGTTGCACTCGTCC  
 GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG  
 816 BGLI, 833 DRD1,  
 ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr  
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCCGCCGAGACT  
 CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAAGTGGGGGGGCTCTGA  
 881 SACI,  
 ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu  
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT  
 TGTCAATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCCTGGTAGAA  
 931 SMAI XMAI,  
 GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln  
 962 GAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCACTTTCTATCCCAG  
 CTTAAAACCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC  
 985 STUI,  
 ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla  
 1022 ACAAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT  
 TGTTTCGTCTACCCCTCTTGGAAGGAATGGACCATCGCATGGTTCCGGTGGCACACGCGA  
 1069 DRA3,  
 ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys  
 1082 AGGGCTCAAGCCCTCCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTGCGCTCAAG

ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle  
1142 CCCACCCTCCATGGGCCAACCCCTGCTATACAGACTGGGCGTGTTCAGAATGAAATC  
GGGTGGGAGGTACCCGGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG

ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal  
1202 ACCCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTCGGCCGACCTGGAGGTC  
TGGGACTGCGTGGGTCACTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGACCTCCAG

ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu  
1262 GTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCCTGGCTGCTTTGGCCGCGTATTGCCTG  
CAGTGCTCGTGGACCCACGAGCAACCGCCGCAGGACCGACGAAACCGGCGCATAACGGAC

1322 SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle  
TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCCGGGAAGCCGGCAATCATA  
AGTTGTCCGACGCACCAAGTATCACCCGTCCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT

ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu  
1382 CCTGACAGGGAAGTCTCTACCGAGAGTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA  
GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCAGGAGAGTCGTGAAT

ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu  
1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTCGGCCTC  
GGCATGTAGCTCGTTCCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAGCCGGAG

1502 LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln  
CTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCCCCTGCTGTCCAGACCAACTGGCAA  
GACGTCTGGCGCAGGGCAGTCCGCTCTCAATAGCGGGGACGACAGGTCTGGTTGACCGTT

1562 LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu  
AAACTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG  
TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCTATGTTATGAAC

AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla  
1622 GCGGGCTTGTC AACGCTGCCTGGTAACCCGCCATTGCTTCATTGATGGCTTTTACAGCT  
CGCCCGAACAGTTGCGACGGACCATTGGGGCGGTAACGAAGTAACTACCGAAAATGTCGA

AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp  
1682 GCTGTCAACGACCCACTAACCCTAGCCAAACCCTCCTCTTCAACATATTGGGGGGGTGG  
CGACAGTGGTGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC

ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla  
 1742 GTGGCTGCCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT  
 CACCGACGGGTCGAGCGCGGGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA  
 ^  
 1794 ESP1,  
 GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr  
 1802 GCGCGCCGCATCGGCAGTGTGGACTGGGGAAGGTCCTCATAGACATCCTTGCAGGGTAT  
 CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCAT  
 ^  
 1802 KAS1 NARI,  
 GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer  
 1862 GCGCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCCTCC  
 CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG  
 ^ ^  
 1878 SACI, 1899 BSPH1,  
 ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly  
 1922 ACGGAGGACCTGGTCAATCTACTGCCCCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC  
 TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG  
 ^  
 1928 TTH3I,  
 ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp  
 1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCGGGCGAGGGGGCAGTGCACTGG  
 CACCAGACACGTCGTTATGACGCGGCCGTGAACCGGGCCCGCTCCCCCGTCACGTCACC  
 ^ ^  
 2004 NAEI, 2017 SMAI XMAI,  
 MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal  
 2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTTCCCCCAGCCTACGTG  
 TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGTGCGTGATGCAC  
 ^ ^  
 2067 SMAI XMAI, 2093 DRA3,  
 ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln  
 2102 CCGGAGAGCGATGCAGCTGCCCCGCTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG  
 GGCCTCTCGCTACGTCGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTC  
 ^ ^  
 2115 PVU2, 2159 ALWN1,  
 LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer  
 2162 CTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTACCACTCCATGCTCCGGTTCC  
 GAGGACTCCGCTGACGTGGTCACCTATTTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG  
 ^ ^  
 2164 MST2, 2220 ECON1,  
 TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu  
 2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA  
 ACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT  
 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr  
 2282 AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCTTTGTGTCCTGCCAGCGGGGTAT  
 TTTTCGATTGAGTACGGTGTGACGGACCCTAGGGGAAACACAGGACGGTCGCGCCCAT  
 ^ ^ ^  
 2285 ESP1, 2300 PVU2, 2310 BAMHI,

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LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle  
2342 AAGGGGGTCTGCGGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC  
TTCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG

ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet  
2402 ACTGGACATGTCAAAACGGGACGATGAGGATCGTCGGTCCTAGGACCTGCAGGAACATG  
TGACCTGTACAGTTTTTGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCCTGTAC  
2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,

TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla  
2462 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCCCTGTACCCCCCTTCTGCG  
ACCTCACCTGGAAGGGGTAATTACGGATGTGGTGCCCCGGGACATGGGGGAAGGACGC  
2480 ASE1, 2497 APAI,

ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln  
2522 CCGAACTACACGTTCCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG  
GGCTTGATGTGCAAGCGGATACCTCCACAGACGTCTCCTTATGCACCTCTATTCCGTC  
2553 PSTI,

ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln  
2582 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCGTGCCAG  
CACCCCCTGAAGGTGATGCACTGCCCATACTGATGACTGTTAGAATTTACGGGCACGGTC  
2594 DRA3,

ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro  
2642 GTCCCATCGCCCGAATTTTTTCACAGAATTGGACGGGGTGGCCTACATAGGTTTGCGCCC  
CAGGGTAGCGGGCTTAAAAAGTGCTTAACCTGCCCCACGCGGATGTATCCAACGCGGG

ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro  
2702 CCCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTCAGAGTAGGACTCCACGAATACCCG  
GGGACGTTGCGGAACGACGCCCTCCTCCATAGTAAGTCTCATCCTGAGGTGCTTATGGGC  
2757 HGIE2,

ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu  
2762 GTAGGGTGCGAATTACCTTGCGAGCCCGAACCGGACGTGGCCGTGTTGACGTCCATGCTC  
CATCCACGCGTTAATGGAACGCTCGGGCTTGCCCTGCACCGGCACAACTGCAGGTACGAG  
2809 AAT2,

ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro  
2822 ACTGATCCCTCCCATATAACAGCAGAGGCGGCCGGGCGAAGGTTGGCGAGGGGATCACCC  
TGACTAGGGAGGGTATATTGTCGTCTCCGCCGGCCCGCTTCCAACCGCTCCCCTAGTGGG  
2850 EAG1 XMA3,

ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys  
2882 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC  
GGGAGACACCGGTGCGAGGAGCCGATCGGTGATAGGCGAGGTAGAGAGTTCCGTTGAACG  
2889 BALI, 2903 NHEI,

ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuTrpArgGlu  
2942 ACCGCTAACCATGACTCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG  
TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGGTTGGAGGATACCTCCGTC  
2966 ESP1, 2969 SACI,  
GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer  
3002 GAGATGGGCGGCCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC  
CTCTACCCGCCGTTGTAGTGGTCCCAACTCAGTCTTTTGTTCACCACTAAGACCTGAGG  
PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu  
3062 TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGCAGAAATCCTG  
AAGCTAGGCGAACACCGCCTCCTCCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC  
3096 BGL2,  
ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro  
3122 CGGAAGTCTCGGAGATTCGCCCAGGCCCTGCCGTTTGGGCGCGGCCGACTATAACCCC  
GCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGGCCTGATATTGGGG  
3143 ALWN1, 3164 EAG1 XMA3,  
ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro  
3182 CCGCTAGTGGAGACGTGAAAAAGCCCGACTACGAACCACCTGTGGTCCATGGCTGCCCG  
GGCGATCACCTCTGCACCTTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGGC  
3217 HGIE2, 3229 NCOI,  
LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu  
3242 CTTCCACCTCCAAAGTCCCCTCCTGTGCCTCCGCCCTCGGAAGAAGCGGACGGTGGTCCCTC  
GAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG  
ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer  
3302 ACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC  
TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG  
3332 SACI, 3346 HIND3,  
SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly  
3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCCGCCCTTCTGGC  
AGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG  
CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro  
3422 TGCCCCCCCCGACTCCGACGCTGAGTCTATTCTCTCCATGCCCCCCTGGAGGGGGGAGCCT  
ACGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA  
3437 EAM11051,  
GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu  
3482 GGGGATCCGGATCTTAGCGACGGGTGATGGTCAACGGTCAGTAGTGAGGCCAACGCGGAG  
CCCCTAGGCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGGTTGCGCCTC  
3484 BAMHI, 3485 BSAB1, 3487 BSPE1,  
AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla  
3542 GATGTCGTGTGCTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCGTGCGCC  
CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGACGCGG

Figure 1 consists of 12 sub-graphs labeled (a) through (l), each showing the growth of *E. coli* O157:H7 in ground beef under different treatment conditions. The y-axis for all graphs is  $\log_{10}$  CFU/g, ranging from 0 to 10. The x-axis is time in hours, ranging from 0 to 120. The graphs show various growth curves, with some treatments showing significant inhibition of growth compared to the control.

- (a) Control: Shows a steady increase in bacterial count from approximately  $10^1$  to  $10^9$  CFU/g over 120 hours.
- (b) Salt: Shows a slight increase in bacterial count from approximately  $10^1$  to  $10^2$  CFU/g over 120 hours.
- (c) Acetic acid: Shows a decrease in bacterial count from approximately  $10^1$  to  $10^0$  CFU/g over 120 hours.
- (d) Lactic acid: Shows a decrease in bacterial count from approximately  $10^1$  to  $10^0$  CFU/g over 120 hours.
- (e) Citric acid: Shows a decrease in bacterial count from approximately  $10^1$  to  $10^0$  CFU/g over 120 hours.
- (f) Propionic acid: Shows a decrease in bacterial count from approximately  $10^1$  to  $10^0$  CFU/g over 120 hours.
- (g) Sorbic acid: Shows a decrease in bacterial count from approximately  $10^1$  to  $10^0$  CFU/g over 120 hours.
- (h) Butyric acid: Shows a decrease in bacterial count from approximately  $10^1$  to  $10^0$  CFU/g over 120 hours.
- (i) Benzoic acid: Shows a decrease in bacterial count from approximately  $10^1$  to  $10^0$  CFU/g over 120 hours.
- (j) Sodium nitrite: Shows a decrease in bacterial count from approximately  $10^1$  to  $10^0$  CFU/g over 120 hours.
- (k) Sodium nitrate: Shows a decrease in bacterial count from approximately  $10^1$  to  $10^0$  CFU/g over 120 hours.
- (l) Sodium lactate: Shows a decrease in bacterial count from approximately  $10^1$  to  $10^0$  CFU/g over 120 hours.

GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr  
4202 GGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG  
CCCAAGAGCATACTATGGGCGACGAAACTGAGGTGTCAGTGACTCTCGCTGTAGGCATGC





4862 AGGGACCAGCTTGAACAGGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA  
TCCCTGGTTCGAACCTTGTCCGGGAGCTAACGCTCTAGATGCCCCGGACGATGAGGTATCTT  
4893 BGL2,  
ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis  
4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTTCACTCCAC  
GGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTCGCGTAAAAGTGAGGTG  
4954 NCOI,  
SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro  
4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAAACCTTGGGGTACCG  
TCAATGAGAGGTCCACTTTAGTTATCCACCGGCGTACGGAGTCTTTTGAACCCCATGGC  
5015 SPHI, 5035 KPNI,  
ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly  
5042 CCCTTGCGAGCTTGGAGACACCGGGCCCGGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA  
GGGAACGCTCGAACCTCTGTGGCCCGGGCCTCGCAGGCGCGATCCGAAGACCGGTCTCCT  
5064 APAI, 5091 BALI,  
GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys  
5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAA  
CCGTCCCGACGGTATACACCGTTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT  
5113 NDEI,  
LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr  
5162 CTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTTCACGGCTGGCTAC  
GAGTGAGGTTATCGCCGGCGACCGGTTCGACCTGAACAGGCCGACCAAGTGCCGACCGATG  
5174 NOTI, 5175 EAG1 XMA3, 5182 BALI, 5186 PVU2,  
SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys  
5222 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCCGCCCCGCTGGATCTGGTTTTGC  
TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCCGGGGCGACCTAGACCAAACG  
5240 DRA3,  
LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn  
5282 CTACTCCTGCTTGTGTCAGGGGTAGGCATCTACCTCCTCCCCAACCGAATGAGCACGAAT  
GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTTGGCTTACTCGTGCTTA  
5295 PSTI,  
ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe  
5342 CCTAAACCTCAAAGAAAGACCAAACGTAACACCAACCGGCGCGCAGGACGTCAAGTTC  
GGATTTGGAGTTTCTTTCTGGTTTGCATTGTGGTTGGCCCGCGCGCTCCTGCAGTTCAAG  
5380 NOTI, 5381 EAG1 XMA3, 5390 AAT2, 5401 SMAI XMAI,  
ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu  
5402 CCGGGTGGCGGTGAGATCGTTGGTGGAGTTTACTTGTGTGCCGCGCAGGGGCCCTAGATTG  
GGCCCCACGCCAGTCTAGCAACCACTCAAATGAACAACGGCGCGTCCCCGGGATCTAAC

5702 AC  
TG

# FIGURE 18 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn  
 2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC  
 TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG  
 ^ ^ ^  
 1 HIND3, 24 NDEI, 52 SCAI,

ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp  
 62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT  
 GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA  
 ^  
 116 CLAI,

ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr  
 122 CCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCACGTACTCCACC  
 GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATGAGGTGG

TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys  
 182 TACGGCAAGTTCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT  
 ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGCAATACTGTATTATTAAACA

AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln  
 242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA  
 CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAGTGGTT

AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal  
 302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC  
 CGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCCGAGGCAG  
 ^  
 303 ALWN1,

ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe  
 362 ACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGGAGAGATCCCTTTT  
 TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA

TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis  
 422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTCAT  
 ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA

SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal  
 482 TCAAAGAAGAAGTGCACGAACCTCGCCGCAAAGCTGGTCGCATTGGGCATCAATGCCGTG  
 AGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC

AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal  
 542 GCCTACTACCGCGGTCTTGACGTGTCCGTCATCCCGACCAGCGGCGATGTTGTGTCGTCGTG  
 CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAGCAGCAC  
 ^ ^  
 550 SAC2, 560 DRD1,

AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn  
 602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT  
 CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA  
 ^  
 615 BSPH1,

00221-624760

662 ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle  
 ACGTGTGTACCCAGACAGTCGATTTACGCCTTGACCCTACCTTCACCATTGAGACAATC  
 TGCACACAGTGGGTCTGTCTCAGCTAAAGTCGGAAGTGGGATGGAAGTGGTAACTCTGTTAG  
 ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys  
 722 ACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGAAG  
 TGCGAGGGGGTTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCCTGACCGTCCCCCTTC  
 ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer  
 782 CCAGGCATCTACAGATTTGTGGCACCAGGGGAGCGCCCCCTCCGGCATGTTTCGACTCGTCC  
 GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG  
 816 BGLI, 833 DRD1,  
 ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr  
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCCGCCGAGACT  
 CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGGCTCTGA  
 881 SACI,  
 ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu  
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT  
 TGTCATCCGATGCTCGCATGTACTTGTGGGCCCCGAAGGGCACACGGTCTCTGGTAGAA  
 931 SMAI XMAI,  
 GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln  
 962 GAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCACTTTCTATCCCAG  
 CTTAAACCCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC  
 985 STUI,  
 ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla  
 1022 ACAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT  
 TGTTTCGTCTCACCCCTCTTGGGAAGGAATGGACCATCGCATGGTTCGGTGGCACACGCGA  
 1069 DRA3,  
 ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys  
 1082 AGGGCTCAAGCCCCCTCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTGCGCTCAAG  
 TCCCGAGTTCGGGGAGGGGGTAGCACCTGGTCTACACCTTCACAACTAAGCGGAGTTC  
 ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle  
 1142 CCCACCCTCCATGGGCCAACACCCCTGCTATACAGACTGGGCGCTGTTTCAAGTAAATC  
 GGGTGGGAGGTACCCGGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG  
 1150 NCOI,  
 ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal  
 1202 ACCCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTGCGCCGACCTGGAGGTC  
 TGGGACTGCGTGGGTCAGTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGACCTCCAG  
 1230 BSPH1, 1234 DRD1, 1237 AVA3, 1245 EAG1 XMA3, 1250 DRD1,  
 ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu  
 1262 GTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCCTGGCTGCTTTGGCCGCGTATTGCCTG

# FIGURE 18 - Page 3

CAGTGTCTCGTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATAACGGAC

SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle  
1322 TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCCGGGAAGCCGGCAATCATA  
AGTTGTCCGACGCACCAGTATCACCCGTCCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT

1369 NAEI,

ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu  
1382 CCTGACAGGGAAGTCCTCTACCGAGAGTTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA  
GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCAGAGAGTCGTGAAT

1385 DRD1,

ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu  
1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTCGGCCTC  
GGCATGTAGCTCGTTCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCGGGAGCCGGAG

LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln  
1502 CTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCCCCTGCTGTCCAGACCACTGGCAA  
GACGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTGACCGTT

1502 PSTI, 1507 TTH3I,

LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu  
1562 AAACCTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG  
TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCTATGTTATGAAC

1565 XHOI, 1586 NDEI,

AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla  
1622 GCGGGCTTGTCAACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT  
CGCCCGAACAGTTGCGACGGACCATTGGGGCGGTAACGAAGTAACCTACCGAAAATGTCGA

1643 BSTE2, 1677 ALWN1 PVU2,

AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp  
1682 GCTGTCAACAGCCCACTAACCCTAGCCAAACCTCCTCTTCAACATATTGGGGGGTGG  
CGACAGTGGTCGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC

ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla  
1742 GTGGCTGCCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT  
CACCGACGGGTGAGCGGGGGGGCCACGGCGATGACGGAACACCCGCGACCGAATCGA

1794 ESP1,

GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr  
1802 GGCGCCGCCATCGGCAGTGTGGACTGGGGAAGTCCCTCATAGACATCCTTGAGGGGTAT  
CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCAT

1802 KAS1 NARI,

GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer  
1862 GGCGCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCCTCC  
CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG

1878 SACI, 1899 BSPH1,

002211-041250

ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly  
1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC  
TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG  
1928 TTH3I,  
ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp  
1982 GTGGTCTGTGCAGCAATACTGCCCGGCACGTTGGCCCGGGCGAGGGGGCAGTGTCAGTGG  
CACCAGACACGTCGTTATGACGGCGCCGTGCAACCGGGCCCCGCTCCCCCGTCACGTACCC  
2004 NAEI, 2017 SMAI XMAI,  
MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal  
2042 ATGAACCGGCTGATAGCCTTCGCCCTCCCGGGGGAACCATGTTTCCCCACGCACTACGTG  
TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGGTGCGTGATGCAC  
2067 SMAI XMAI, 2093 DRA3,  
ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln  
2102 CCGGAGAGCGATGCAGCTGCCCCGCGTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG  
GGCCTCTCGCTACGTCGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTC  
2115 PVU2, 2159 ALWN1,  
LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer  
2162 CTCCTGAGGCGACTGCACCAGTGGATAAGCTCGGAGTGTACCACTCCATGCTCCGGTTCC  
GAGGACTCCGCTGACGTGGTCACCTATTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG  
2164 MST2, 2220 ECON1,  
TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu  
2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA  
ACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT  
LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr  
2282 AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCCTTTGTGTCTGCCAGCGCGGGTAT  
TTTCGATTGAGTACGGTGTGACGGACCCTAGGGGAAACACAGGACGGTCGCGCCCAT  
2285 ESP1, 2300 PVU2, 2310 BAMHI,  
LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle  
2342 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC  
TTCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG  
ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet  
2402 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCTTAGGACCTGCAGGAACATG  
TGACCTGTACAGTTTTTGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCCTTGATC  
2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,  
TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla  
2462 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCCCTGTACCCCCCTCCTGCG  
ACCTCACCTGGAAGGGGTAAATTACGGATGTGGTCCCGGGGACATGGGGGGAAGGACGC  
2480 ASE1, 2497 APAI,

Detailed description of Figure 6: This figure consists of ten horizontal panels, each representing a different gene or set of genes. Each panel contains two rows of rectangular spots, which are DNA microarrays. The spots are arranged in columns and are labeled with gene names and associated numerical values. 
 - Panel (a) labels include GADD45, BAX, BCL2L1, BCL2, CASP8, CASP9, CASP10, CASP11, CASP12, CASP13, CASP14, CASP15, CASP16, CASP17, CASP18, CASP19, CASP20, CASP21, CASP22, CASP23, CASP24, CASP25, CASP26, CASP27, CASP28, CASP29, CASP30, CASP31, CASP32, CASP33, CASP34, CASP35, CASP36, CASP37, CASP38, CASP39, CASP40, CASP41, CASP42, CASP43, CASP44, CASP45, CASP46, CASP47, CASP48, CASP49, CASP50, CASP51, CASP52, CASP53, CASP54, CASP55, CASP56, CASP57, CASP58, CASP59, CASP60, CASP61, CASP62, CASP63, CASP64, CASP65, CASP66, CASP67, CASP68, CASP69, CASP70, CASP71, CASP72, CASP73, CASP74, CASP75, CASP76, CASP77, CASP78, CASP79, CASP80, CASP81, CASP82, CASP83, CASP84, CASP85, CASP86, CASP87, CASP88, CASP89, CASP90, CASP91, CASP92, CASP93, CASP94, CASP95, CASP96, CASP97, CASP98, CASP99, CASP100.
 - Panel (b) labels include p53, Bcl-2, Bcl-xL, Bcl-2L1, Bcl-2L2, Bcl-2L3, Bcl-2L4, Bcl-2L5, Bcl-2L6, Bcl-2L7, Bcl-2L8, Bcl-2L9, Bcl-2L10, Bcl-2L11, Bcl-2L12, Bcl-2L13, Bcl-2L14, Bcl-2L15, Bcl-2L16, Bcl-2L17, Bcl-2L18, Bcl-2L19, Bcl-2L20, Bcl-2L21, Bcl-2L22, Bcl-2L23, Bcl-2L24, Bcl-2L25, Bcl-2L26, Bcl-2L27, Bcl-2L28, Bcl-2L29, Bcl-2L30, Bcl-2L31, Bcl-2L32, Bcl-2L33, Bcl-2L34, Bcl-2L35, Bcl-2L36, Bcl-2L37, Bcl-2L38, Bcl-2L39, Bcl-2L40, Bcl-2L41, Bcl-2L42, Bcl-2L43, Bcl-2L44, Bcl-2L45, Bcl-2L46, Bcl-2L47, Bcl-2L48, Bcl-2L49, Bcl-2L50, Bcl-2L51, Bcl-2L52, Bcl-2L53, Bcl-2L54, Bcl-2L55, Bcl-2L56, Bcl-2L57, Bcl-2L58, Bcl-2L59, Bcl-2L60, Bcl-2L61, Bcl-2L62, Bcl-2L63, Bcl-2L64, Bcl-2L65, Bcl-2L66, Bcl-2L67, Bcl-2L68, Bcl-2L69, Bcl-2L70, Bcl-2L71, Bcl-2L72, Bcl-2L73, Bcl-2L74, Bcl-2L75, Bcl-2L76, Bcl-2L77, Bcl-2L78, Bcl-2L79, Bcl-2L80, Bcl-2L81, Bcl-2L82, Bcl-2L83, Bcl-2L84, Bcl-2L85, Bcl-2L86, Bcl-2L87, Bcl-2L88, Bcl-2L89, Bcl-2L90, Bcl-2L91, Bcl-2L92, Bcl-2L93, Bcl-2L94, Bcl-2L95, Bcl-2L96, Bcl-2L97, Bcl-2L98, Bcl-2L99, Bcl-2L100.
 - Panel (c) labels include p53, Bcl-2, Bcl-xL, Bcl-2L1, Bcl-2L2, Bcl-2L3, Bcl-2L4, Bcl-2L5, Bcl-2L6, Bcl-2L7, Bcl-2L8, Bcl-2L9, Bcl-2L10, Bcl-2L11, Bcl-2L12, Bcl-2L13, Bcl-2L14, Bcl-2L15, Bcl-2L16, Bcl-2L17, Bcl-2L18, Bcl-2L19, Bcl-2L20, Bcl-2L21, Bcl-2L22, Bcl-2L23, Bcl-2L24, Bcl-2L25, Bcl-2L26, Bcl-2L27, Bcl-2L28, Bcl-2L29, Bcl-2L30, Bcl-2L31, Bcl-2L32, Bcl-2L33, Bcl-2L34, Bcl-2L35, Bcl-2L36, Bcl-2L37, Bcl-2L38, Bcl-2L39, Bcl-2L40, Bcl-2L41, Bcl-2L42, Bcl-2L43, Bcl-2L44, Bcl-2L45, Bcl-2L46, Bcl-2L47, Bcl-2L48, Bcl-2L49, Bcl-2L50, Bcl-2L51, Bcl-2L52, Bcl-2L53, Bcl-2L54, Bcl-2L55, Bcl-2L56, Bcl-2L57, Bcl-2L58, Bcl-2L59, Bcl-2L60, Bcl-2L61, Bcl-2L62, Bcl-2L63, Bcl-2L64, Bcl-2L65, Bcl-2L66, Bcl-2L67, Bcl-2L68, Bcl-2L69, Bcl-2L70, Bcl-2L71, Bcl-2L72, Bcl-2L73, Bcl-2L74, Bcl-2L75, Bcl-2L76, Bcl-2L77, Bcl-2L78, Bcl-2L79, Bcl-2L80, Bcl-2L81, Bcl-2L82, Bcl-2L83, Bcl-2L84, Bcl-2L85, Bcl-2L86, Bcl-2L87, Bcl-2L88, Bcl-2L89, Bcl-2L90, Bcl-2L91, Bcl-2L92, Bcl-2L93, Bcl-2L94, Bcl-2L95, Bcl-2L96, Bcl-2L97, Bcl-2L98, Bcl-2L99, Bcl-2L100.
 - Panel (d) labels include p53, Bcl-2, Bcl-xL, Bcl-2L1, Bcl-2L2, Bcl-2L3, Bcl-2L4, Bcl-2L5, Bcl-2L6, Bcl-2L7, Bcl-2L8, Bcl-2L9, Bcl-2L10, Bcl-2L11, Bcl-2L12, Bcl-2L13, Bcl-2L14, Bcl-2L15, Bcl-2L16, Bcl-2L17, Bcl-2L18, Bcl-2L19, Bcl-2L20, Bcl-2L21, Bcl-2L22, Bcl-2L23, Bcl-2L24, Bcl-2L25, Bcl-2L26, Bcl-2L27, Bcl-2L28, Bcl-2L29, Bcl-2L30, Bcl-2L31, Bcl-2L32, Bcl-2L33, Bcl-2L34, Bcl-2L35, Bcl-2L36, Bcl-2L37, Bcl-2L38, Bcl-2L39, Bcl-2L40, Bcl-2L41, Bcl-2L42, Bcl-2L43, Bcl-2L44, Bcl-2L45, Bcl-2L46, Bcl-2L47, Bcl-2L48, Bcl-2L49, Bcl-2L50, Bcl-2L51, Bcl-2L52, Bcl-2L53, Bcl-2L54, Bcl-2L55, Bcl-2L56, Bcl-2L57, Bcl-2L58, Bcl-2L59, Bcl-2L60, Bcl-2L61, Bcl-2L62, Bcl-2L63, Bcl-2L64, Bcl-2L65, Bcl-2L66, Bcl-2L67, Bcl-2L68, Bcl-2L69, Bcl-2L70, Bcl-2L71, Bcl-2L72, Bcl-2L73, Bcl-2L74, Bcl-2L75, Bcl-2L76, Bcl-2L77, Bcl-2L78, Bcl-2L79, Bcl-2L80, Bcl-2L81, Bcl-2L82, Bcl-2L83, Bcl-2L84, Bcl-2L85, Bcl-2L86, Bcl-2L87, Bcl-2L88, Bcl-2L89, Bcl-2L90, Bcl-2L91, Bcl-2L92, Bcl-2L93, Bcl-2L94, Bcl-2L95, Bcl-2L96, Bcl-2L97, Bcl-2L98, Bcl-2L99, Bcl-2L100.
 - Panel (e) labels include p53, Bcl-2, Bcl-xL, Bcl-2L1, Bcl-2L2, Bcl-2L3, Bcl-2L4, Bcl-2L5, Bcl-2L6, Bcl-2L7, Bcl-2L8, Bcl-2L9, Bcl-2L10, Bcl-2L11, Bcl-2L12, Bcl-2L13, Bcl-2L14, Bcl-2L15, Bcl-2L16, Bcl-2L17, Bcl-2L18, Bcl-2L19, Bcl-2L20, Bcl-2L21, Bcl-2L22, Bcl-2L23, Bcl-2L24, Bcl-2L25, Bcl-2L26, Bcl-2L27, Bcl-2L28, Bcl-2L29, Bcl-2L30, Bcl-2L31, Bcl-2L32, Bcl-2L33, Bcl-2L34, Bcl-2L35, Bcl-2L36, Bcl-2L37, Bcl-2L38, Bcl-2L39, Bcl-2L40, Bcl-2L41, Bcl-2L42, Bcl-2L43, Bcl-2L44, Bcl-2L45, Bcl-2L46, Bcl-2L47, Bcl-2L48, Bcl-2L49, Bcl-2L50, Bcl-2L51, Bcl-2L52, Bcl-2L53, Bcl-2L54, Bcl-2L55, Bcl-2L56, Bcl-2L57, Bcl-2L58, Bcl-2L59, Bcl-2L60, Bcl-2L61, Bcl-2L62, Bcl-2L63, Bcl-2L64, Bcl-2L65, Bcl-2L66, Bcl-2L67, Bcl-2L68, Bcl-2L69, Bcl-2L70, Bcl-2L71, Bcl-2L72, Bcl-2L73, Bcl-2L74, Bcl-2L75, Bcl-2L76, Bcl-2L77, Bcl-2L78, Bcl-2L79, Bcl-2L80, Bcl-2L81, Bcl-2L82, Bcl-2L83, Bcl-2L84, Bcl-2L85, Bcl-2L86, Bcl-2L87, Bcl-2L88, Bcl-2L89, Bcl-2L90, Bcl-2L91, Bcl-2L92, Bcl-2L93, Bcl-2L94, Bcl-2L95, Bcl-2L96, Bcl-2L97, Bcl-2L98, Bcl-2L99, Bcl-2L100.
 - Panel (f) labels include p53, Bcl-2, Bcl-xL, Bcl-2L1, Bcl-2L2, Bcl-2L3, Bcl-2L4, Bcl-2L5, Bcl-2L6, Bcl-2L7, Bcl-2L8, Bcl-2L9, Bcl-2L10, Bcl-2L11, Bcl-2L12, Bcl-2L13, Bcl-2L14, Bcl-2L15, Bcl-2L16, Bcl-2L17, Bcl-2L18, Bcl-2L19, Bcl-2L20, Bcl-2L21, Bcl-2L2

ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln  
2522 CCGAACTACACGTTCCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG  
GGCTTGATGTGCAAGCGCGATACCTCCCACAGACGTCTCCTTATGCACCTCTATTCCGTC  
2553 PSTI,  
ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln  
2582 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCGTGCCAG  
CACCCCTGAAGGTGATGCACTGCCCATACTGATGACTGTTAGAATTTACGGGCACGGTC  
2594 DRA3,  
ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro  
2642 GTCCCATCGCCCCGAATTTTTACAGAATTGGACGGGGTGCGCCTACATAGGTTTGCGCCC  
CAGGGTAGCGGGCTTAAAAAGTGTCTTAACCTGCCCCACGCGGATGTATCCAAACGCGGG  
ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro  
2702 CCCTGCAAGCCCTTGTCTGCGGGAGGAGGTATCATTCAGAGTAGGACTCCACGAATACCCG  
GGGACGTTGCGGGAACGACGCCCTCCTCCATAGTAAGTCTCATCCTGAGGTGCTTATGGGC  
2757 HGIE2,  
ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu  
2762 GTAGGGTCGAATTACCTTGCGAGCCCGAACC GGACGTGGCCGTGTTGACGTCCATGCTC  
CATCCCAGCGTTAATGGAACGCTCGGGCTTGGCCTGCACCGGCACAAC TG CAGGTACGAG  
2809 AAT2,  
ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro  
2822 ACTGATCCCTCCCATATAACAGCAGAGGCGGCCGGCGGAAGTTGGCGAGGGGATCACCC  
TGACTAGGGAGGGTATATTGTCGTCTCCGCCGGCCCGCTTCCAACCGCTCCCCTAGTGGG  
2850 EAG1 XMA3,  
ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys  
2882 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC  
GGGAGACACCGGTGCGAGGAGCCGATCGGTCGATAGGCGAGGTAGAGAGTTCCGTTGAACG  
2889 BALI, 2903 NHEI,  
ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrpArgGln  
2942 ACCGCTAACCATGACTCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG  
TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGTTTGGAGGATACCTCCGTC  
2966 ESP1, 2969 SACI,  
GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer  
3002 GAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC  
CTCTACCCGCCGTTGTAGTGGTCCCAACTCAGTCTTTTGTTCACCACTAAGACCTGAGG  
3062 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu  
TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGCAGAAATCCTG  
AAGCTAGGCGAACACCGCCTCCTCCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC  
3096 BGL2,  
ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro

3122 CGGAAGTCTCGGAGATTTCGCCAGGCCCTGCCCGTTTGGGCGCGGCCGGACTATAACCCCGCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGCCTGATATTGGGG  
3143 ALWN1, 3164 EAG1 XMA3,  
ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro  
3182 CCGCTAGTGGAGACGTGGAAAAAGCCCCGACTACGAACCACCTGTGGTCCATGGCTGCCCGGGCGATCACCTCTGCACCTTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGGC  
3217 HGIE2, 3229 NCOI,  
LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu  
3242 CTTCCACCTCCAAAGTCCCTCCTGTGCCTCCGCTCGGAAGAAGCGGACGGTGGTCCCTCGAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG  
3302 ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSerACTGAATCAACCCTATCTACTGCCTTGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCTTGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTTCGAAACCGTCGAGG  
3332 SAC1, 3346 HIND3,  
SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly  
3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCCCCCCTTCTGGCAGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG  
3422 CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluProTGCCCCCCCCGACTCCGACGCTGAGTCCTATTCTCCATGCCCCCCCCTGGAGGGGGGAGCCTACGGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA  
3437 EAM11051,  
GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu  
3482 GGGGATCCGGATCTTAGCGACGGGTGATGGTCAACGGTCAGTAGTGAGGCCAACGCGGAGCCCCTAGGCCCTAGAATCGCTGCCCAGTACCAGTTGCCAGTCATCACTCCGGTTGCGCCTC  
3484 BAMHI, 3485 BSAB1, 3487 BSPE1,  
AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla  
3542 GATGTCGTGTGCTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCGTGCGCCCTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCTGAGCAGTGGGGCACGCGG  
3589 DRA3, 3600 SAC2,  
AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn  
3602 GCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTCACCACAATCGCCTTCTTGTCTTTGACGGGTAGTTACGTGATTGCTTGAGCAACGATGCAGTGGTGTTA  
3611 ALWN1, 3655 PFLM1,  
LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp  
3662 TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACATTTGACAACCACATAAGGTGGTGGAGTGCGTCACGAACGGTTTCCGTCTTCTTTTCAGTGTAAGCTG  
3681 DRA3,  
ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla  
3722 AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGGC



4382 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys  
TATCGCAGGTGCCGCGAGCGGCGTACTGACAACTAGCTGTGGTAACACCCTCACTTGC  
ATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTGTGGGAGTGAACG

TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal  
 4442 TACATCAAGGCCCGGGCAGCCTGTCTGAGCCGCAGGGCTCCAGGACTGCACCATGCTCGTG  
 ATGTAGTTCCGGGCCCGTCGGACAGCTCGGCGTCCCGAGGTCCTGACGTGGTACGAGCAC  
 ^  
 4452 SMAI XMAI,  
 CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer  
 4502 TGTGGCGACGACTTAGTCTGTTATCTGTGAAAGCGCGGGGGTCCAGGAGGACGCGGCGAGC  
 ACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCTCTCTGCGCCGCTCG  
 ^ ^  
 4508 DRD1, 4511 TTH3I,  
 LeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspProProGln  
 4562 CTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCCTGGGGACCCCCACAA  
 GACTCTCGGAAGTGCCTCCGATACTGGTCCATGAGGCGGGGGGACCCCTGGGGGGTGT  
 ProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAlaHisAsp  
 4622 CCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTCTGCTCGCCACGAC  
 GGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGGGTGTCT  
 ^  
 4637 SACI,  
 GlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAlaArgAla  
 4682 GGCGCTGGAAAGAGGGTCTACTACCTACCCGTGACCCACAAACCCCTCGCGAGAGCT  
 CCGCGACCTTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGGAGCGCTCTCGA  
 ^  
 4731 NRUI,  
 AlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIleMetPhe  
 4742 GCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATCATGTTT  
 CGCACCTCTGTCTTCTGTGTGAGGTCTAGTTAAGGACCGATCCGTTGTATTAGTACAAA  
 AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla  
 4802 GCCCCACACTGTGGGCGAGGATGATACTGATGACCCATTTCTTTAGCGTCTTTATAGCC  
 CGGGGGTGTGACACCCGCTCTACTATGACTACTGGGTAAAGAAATCGCAGGAATATCGG  
 ^ ^  
 4806 PFLM1, 4807 DRA3,  
 ArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSerIleGlu  
 4862 AGGGACAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA  
 TCCCTGGTTCGAACCTGTCCGGGAGCTAACGCTCTAGATGCCCCGACGATGAGGTATCTT  
 ^  
 4893 BGL2,  
 ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis  
 4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC  
 GGTGACCTAGATGGAGTTAGTAAGTTTCTGAGGTACCGAGTCCGCTAAAAGTGAGGTG  
 ^  
 4954 NCOI,  
 SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro  
 4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAAACCTTGGGGTACCG  
 TCAATGAGAGGTCCACTTTAGTTATCCACCGCGGTACGGAGTCTTTTGAACCCCATGGC  
 ^ ^  
 5015 SPHI, 5035 KPNI,

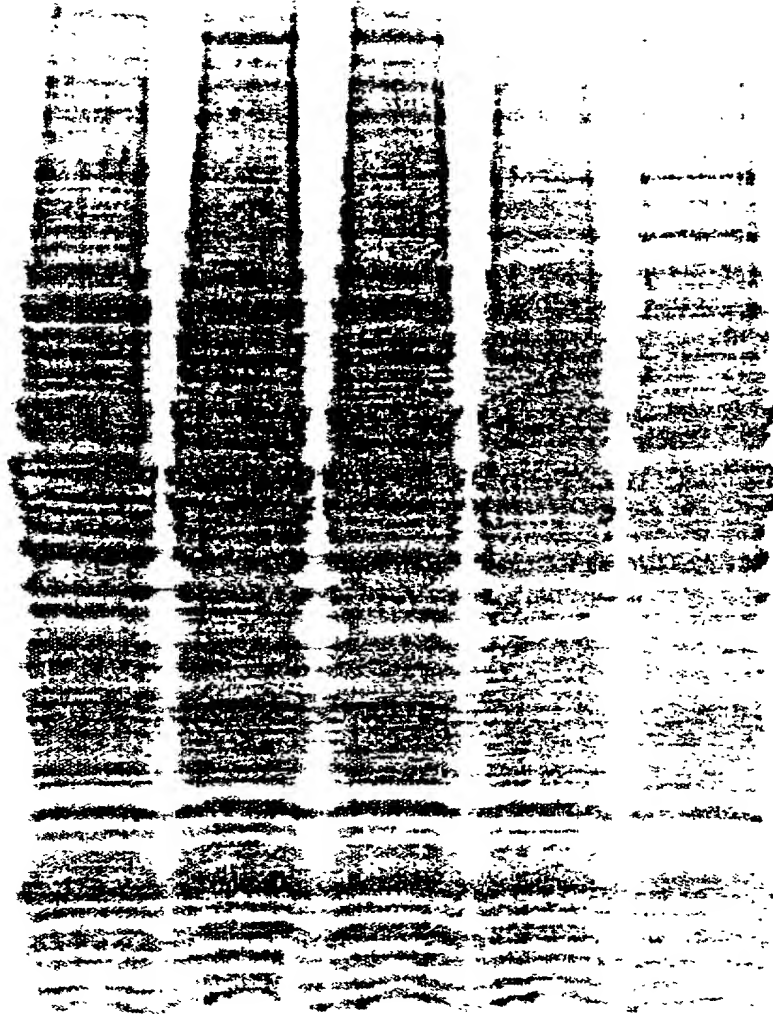
# FIGURE 18 - Page 9

5042 ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly  
 CCCTTGCGAGCTTGGAGACACCGGGCCCGGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA  
 GGAACGCTCGAACCTCTGTGGCCCGGCCCTCGCAGGCGCGATCCGAAGACCGGTCTCCT  
 5064 APAI, 5091 BALI,  
 5102 GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys  
 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAAA  
 CCGTCCCCGACGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT  
 5113 NDEI,  
 5162 LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr  
 CTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTCACGGCTGGCTAC  
 GAGTGAGGTTATCGCCGGCGACCGGTTCGACCTGAACAGGCGGACCAAGTGCCGACCGATG  
 5174 NOTI, 5175 EAG1 XMA3, 5182 BALI, 5186 PVU2,  
 5222 SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys  
 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCCCGGCCCGCTGGATCTGGTTTTGC  
 TCGCCCCCTCTGTAAATAGTGTGCGCACAGAGTACGGGCGGGGCGACCTAGACCAAAACG  
 5240 DRA3,  
 5282 LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn  
 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCCAACCGAATGAGCAGGAAT  
 GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTTACTCGTGCTTA  
 5295 PSTI,  
 5342 ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe  
 CCTAAACCTCAAAGAAAGACCAAACGTAACACCAACCGGCGGCCGAGGACGTCAAGTTC  
 GGATTTGGAGTTTCTTTCTGGTTTGCAATTGTGGTTGGCCGCGCGCGTCTGCAGTTCAAG  
 5380 NOTI, 5381 EAG1 XMA3, 5390 AAT2, 5401 SMAI XMAI,  
 5402 ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu  
 CCGGGTGGCGGTGAGATCGTTGGTGGAGTTTACTTGTGCGCGCAGGGGGCCCTAGATTG  
 GGCCACCGCCAGTCTAGCAACCACCTCAAATGAACAACGGCGCGTCCCCGGGATCTAAC  
 5449 APAI,  
 5462 GlyValArgAlaThrArgLysThrSerGluArgSerGlnProArgGlyArgArgGlnPro  
 GGTGTGCGCGCGACGAGAAAGACTTCCGAGCGGTGCAACCTCGAGGTAGACGTGAGCCT  
 CCACACGCGCGCTGCTCTTTCTGAAGGCTCGCCAGCGTTGGAGCTCCATCTGCAGTCGGA  
 5467 BSSH2, 5478 XMNI, 5502 XHOI, 5511 AAT2,  
 5522 IleProLysAlaArgArgProGluGlyArgThrTrpAlaGlnProGlyTyrProTrpPro  
 ATCCCCAAGGCTCGTTCGGCCCGAGGGCAGGACCTGGGCTCAGCCCGGGTACCCTTGGCCCC  
 TAGGGGTTCCGAGCAGCCGGGCTCCCGTCTGGACCCGAGTCGGGCCCCATGGGAACCGG  
 5548 ALWN1, 5558 ESP1, 5564 SMAI XMAI, 5568 KPNI,  
 5582 LeuTyrGlyAsnGluGlyCysGlyTrpAlaGlyTrpLeuLeuSerProArgGlySerArg  
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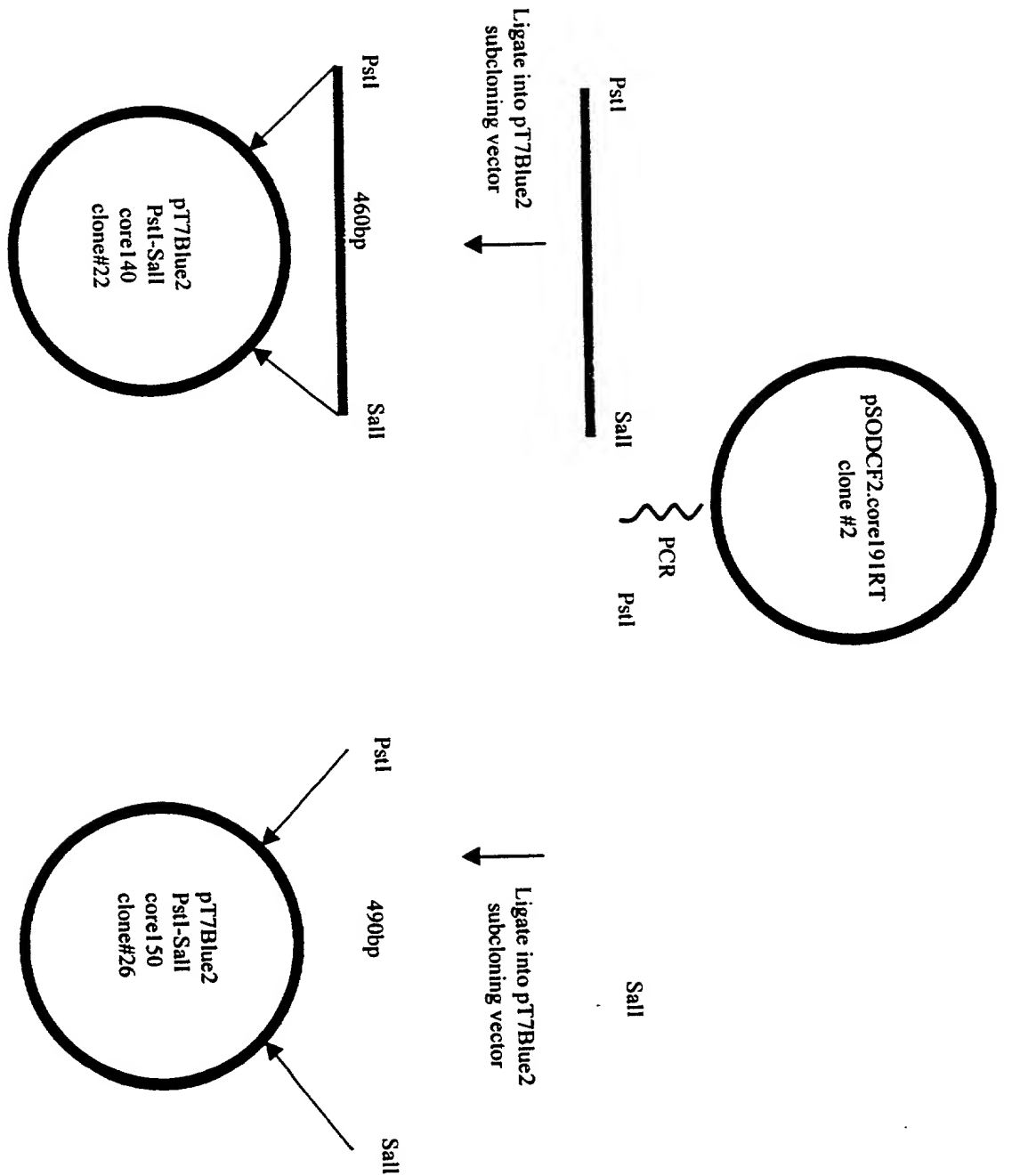
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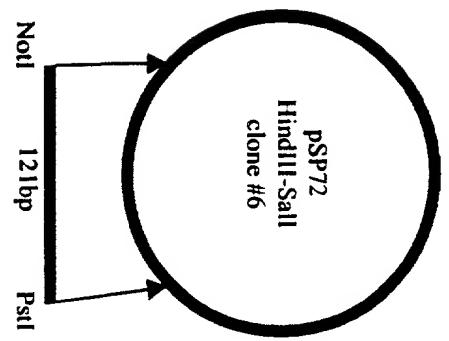


FIGURE 19

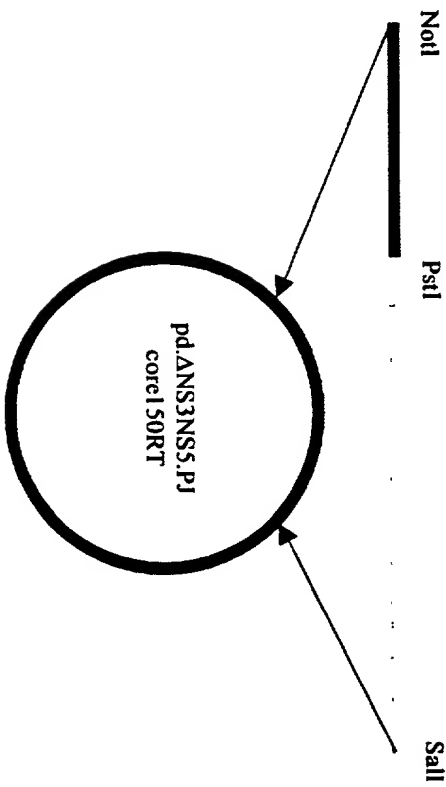
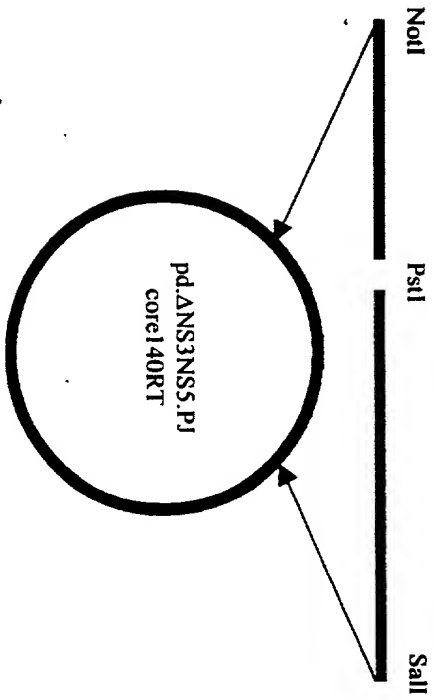


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Ligate fragments into pd.NS3NSS5.PJ  
NotI-Sall cloning vector.



# FIGURE 21 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn  
2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC  
TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG  
^ ^ ^  
1 HIND3, 24 NDEI, 52 SCAI,  
ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp  
62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT  
GGGAGACAACGACGTTGTGACCCGAAACCAGAATGTACAGGTTCCGAGTACCCCTAGCTA  
^  
116 CLAI,  
ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr  
122 CCTAACATCAGGACCGGGTGAGAACAATTACCACTGGCAGCCCCATCAGTACTCCACC  
GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATGAGGTGG  
TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys  
182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT  
ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGCGAATACTGTATTATTAAACA  
AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln  
242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA  
CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAGTGGTT  
AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal  
302 GCAGAGACTGCGGGGCGGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC  
CGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCAG  
^  
303 ALWN1,  
ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe  
362 ACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGGAGAGATCCCTTTT  
TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA  
TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis  
422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGGAGACATCTCATCTTCTGTCAT  
ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA

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TCCCCGAGTTCGGGGAGGGGGGTAGCACCCCTGGTCTACACCTTCACAAACTAAAGCGGAGTTC

ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle  
1142 CCCACCCTCCATGGGCCAACACCCTGCTATACAGACTGGGCGCTGTTCAGAATGAAATC  
GGGTGGGAGGTACCCGGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG  
1150 NCOI,

ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal  
1202 ACCCTGACGCACCCAGTCAACAAATACATCATGACATGCATGTCTGGGCCGACCTGGAGGTC  
TGGGACTGCGTGGGTCACTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGACCTCCAG  
1230 BSPH1, 1234 DRD1, 1237 AVA3, 1245 EAG1 XMA3, 1250 DRD1,

ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu  
1262 GTCACGAGCACCTGGGTGCTCGTTGGCGGGCGTCCTGGCTGCTTTGGCCGCGTATTGCCTG  
CAGTGCTCGTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATAACGGAC

SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle  
1322 TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCGGGAAGCCGGCAATCATA  
AGTTGTCCGACGCACCACTATCACCCGTCCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT  
1369 NAEI,

ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu  
1382 CCTGACAGGGAAGTCCTCTACCGAGAGTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA  
GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCAGGAGAGTCGTGAAT  
1385 DRD1,

ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu  
1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTCGGCCCTC  
GGCATGTAGCTCGTTCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAGCCGGAG

LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln  
1502 CTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCCCCTGCTGTCCAGACCAACTGGCAA  
GACGCTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTGACCGTT  
1502 PSTI, 1507 TTH3I,

LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu  
1562 AAACCTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG  
TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCTATGTTATGAAC  
1565 XHOI, 1586 NDEI,

AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla  
1622 GCGGGCTTGTCACCGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT  
CGCCCGAACAGTTGCGACGGACCATTGGGGCGGTAACGAAGTAACTACCGAAAATGTGCA  
1643 BSTE2, 1677 ALWN1 PVU2,

AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp  
1682 GCTGTCAACAGCCCACTAACCCTAGCCAAACCCTCCTCTCAACATATTGGGGGGGTGG  
CGACAGTGGTGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC

ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla  
1742 GTGGCTGCCAGCTCGCCGCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT  
CACCGACGGGTCGAGCGGCGGGGGCCACGGCGATGACGGAACACCCGCGACCGAATCGA  
1794 ESP1,  
GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr  
1802 GGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCCCTCATAGACATCCTTGCAGGGTAT  
CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCATA  
1802 KAS1 NARI,  
GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer  
1862 GGCGCGGGCGTGCGGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCTCC  
CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG  
1878 SACI, 1899 BSPH1,  
ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly  
1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC  
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1928 TTH3I,  
ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp  
1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCCGGGCGAGGGGGCAGTGCAGTGG  
CACCAGACACGTCGTTATGACGCGGCGGTGCAACCGGGCCCGCTCCCCCGTCACGTCACC  
2004 NAEI, 2017 SMAI XMAI,  
MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal  
2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGGAACCATGTTTCCCCACGCACTACGTG  
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2067 SMAI XMAI, 2093 DRA3,  
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2102 CCGGAGAGCGATGCAGCTGCCGCGTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG  
GGCCTCTCGCTACGTCGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTG  
2115 PVU2, 2159 ALWN1,  
LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer  
2162 CTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTACCACTCCATGCTCCGGTTCC  
GAGGACTCCGCTGACGTGGTCACCTATTTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG  
2164 MST2, 2220 ECON1,  
TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu  
2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA  
ACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT  
2282 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr  
AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCCTTTGTGTCTGCCAGCGCGGGTAT  
TTTCGATTTCGAGTACGGTGTGACGGACCCCTAGGGGAAACACAGGACGGTTCGCGCCCAT  
2285 ESP1, 2300 PVU2, 2310 BAMHI,

2342 LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle  
 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC  
 TTCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG  
 ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet  
 2402 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCTAGGACCTGCAGGAACATG  
 TGACCTGTACAGTTTTTGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCCTTGTAC  
 2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,  
 TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla  
 2462 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCCCTGTACCCCCCTTCTGCG  
 ACCTCACCTGGAAGGGGTAATTACGGATGTGGTGCCCGGGGACATGGGGGAAGGACGC  
 2480 ASE1, 2497 APAI,  
 ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln  
 2522 CCGAACTACACGTTTCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG  
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 2553 PSTI,  
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 2582 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCGTGCCAG  
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 2594 DRA3,  
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 ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu  
 2762 GTAGGGTCGCAATTACCTTGCGAGCCCGAACCGGACGTGGCCGTGTTGACGTCCATGCTC  
 CATCCCAGCGTTAATGGAACGCTCGGGCTTGCCCTGCACCGGCACAACTGCAGGTACGAG  
 2809 AAT2,  
 ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro  
 2822 ACTGATCCCTCCCATATAACAGCAGAGGCGGCCGGGCGAAGGTTGGCGAGGGGATCACCC  
 TGACTAGGGAGGGTATATTGTCGTCTCCGCCGCGCCGCTTCCAACCGCTCCCCTAGTGGG  
 2850 EAG1 XMA3,  
 ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys  
 2882 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC  
 GGGAGACACCGGTCGAGGAGCCGATCGGTCGATAGGCGAGGTAGAGAGTTCGGTTGAACG  
 2889 BALI, 2903 NHEI,

ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrpArgGin  
 2942 ACCGCTAACCATGACTCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAT  
 TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGTTGGAGGATACCTCCGTC  
 ^ ^  
 2966 ESP1, 2969 SACI,  
 GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer  
 3002 GAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC  
 CTCTACCCGCCGTTGTAGTGGTCCCAACTCAGTCTTTTGTTCACCACTAAGACCTGAGG  
 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu  
 3062 TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGCAGAAATCCTG  
 AAGCTAGGCGAACACCGCCTCCTCCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC  
 ^  
 3096 BGL2,  
 ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro  
 3122 CGGAAGTCTCGGAGATTGCCCCAGGCCCTGCCCGTTTGGGCGCGGCCGGACTATAACCCC  
 GCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGGCCTGATATTGGGG  
 ^ ^  
 3143 ALWN1, 3164 EAG1 XMA3,  
 ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro  
 3182 CCGCTAGTGGAGACGTGGAAAAAGCCCGACTACGAACCACCTGTGGTCCATGGCTGCCCG  
 GGCGATCACCTCTGCACCTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGGC  
 ^ ^  
 3217 HGIE2, 3229 NCOI,  
 LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu  
 3242 CTTCCACCTCCAAAGTCCCCTCCTGTGCCTCCGCCCTCGGAAGAAGCGGACGGTGGTCCCTC  
 GAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG  
 ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer  
 3302 ACTGAATCAACCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC  
 TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG  
 ^ ^  
 3332 SACI, 3346 HIND3,  
 SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly  
 3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCCGCCCTTCTGGC  
 AGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG  
 CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro  
 3422 TGCCCCCCCCGACTCCGACGCTGAGTCCTATTCCTCCATGCCCCCCTGGAGGGGGAGCCT  
 ACGGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA  
 ^  
 3437 EAM11051,  
 GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu  
 3482 GGGGATCCGGATCTTAGCGACGGGTGATGGTCAACGGTCAGTAGTGAGGCCAACGCGGAG  
 CCCCTAGGCCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGTTGCGCCTC  
 ^ ^ ^  
 3484 BAMHI, 3485 BSAB1, 3487 BSPE1,  
 AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla  
 3542 GATGTCGTGTGCTGCTCAATGTCTTACTCTTGACAGGCGCACTCGTCACCCCGTGCGCC  
 CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGGCACGCGG

3589 DRA3, 3600 SAC2,

3602 AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn  
GCGGAAGAACAGAACTGCCCCATCAATGCACTAAGCAACTCGTTGCTACGTCACCACAAT  
CGCCTTCTTGTCTTTGACGGGTAGTTACGTGATTGCTTGAGCAACGATGCAGTGGTGTTA  
^ ^

3611 ALWN1, 3655 PFLM1,

3662 LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp  
TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACATTTGAC  
AACCACATAAGGTGGTGGAGTGCGTCACGAACGGTTTCCGTCTTCTTTCAGTGTAAGCTG  
^

3681 DRA3,

3722 ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla  
AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGCG  
TCTGACGTTCAAGACCTGTCGGTAATGGTCTGTCATGAGTTCTCCAATTTTCGTCGCCGC

3782 SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis  
TCAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGACGCTGACGCCCCACAC  
AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTCGGACTGCGGGGGTGTG  
^

3816 HIND3,

3842 SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla  
TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAGACGTCCGTTGCCATGCCAGAAAGGCC  
AGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCTTCCGG  
^ ^

3875 AAT2, 3890 BGLI,

3902 ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp  
GTAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAACACCAATAGAC  
CATTGGGTGTAGTTGAGGCACACCTTCTGGAAGACCTTCTGTTACATTGTGTTATCTG

3962 ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys  
ACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTTCAGCCTGAGAAGGGGGTTCGTAAG  
TGATGGTAGTACCGATTCTTGCTCCAAAAGACGCAAGTCGGACTCTTCCCCCAGCATTC

4022 ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu  
CCAGCTCGTCTCATCGTGTCCCCGATCTGGGCGTGCGCGTGTGCGAAAAGATGGCTTTG  
GGTCGAGCAGAGTAGCACAAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTACCGAAAC

4082 TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr  
TACGACGTGGTTACAAAGCTCCCTTGGCCGTGATGGGAAGCTCCTACGGATTCCAATAC  
ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAGGTTATG

4142 SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet  
TCACCAGGACAGCGGGTTGAATTCCTCGTGCAAGCGTGGAAGTCCAAGAAAACCCCAATG  
AGTGGTCTGTGCGCCCACTTAAGGAGCACGTTTCGCACCTTCAGGTTCTTTTGGGGTTAC  
^

4160 ECORI,

4202 GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr  
GGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG  
CCCAAGAGCATACTATGGGCGACGAACTGAGGTGTCAGTGAAGTCTCGCTGTAGGCATGC  
^ ^

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4229 DRD1, 4236 ALWN1,

4262 GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer  
GAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCAAGCCCGGTGGCCATCAAGTCC  
CTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTTCGGGCGCACCGGTAGTTCAGG

4301 BGLI, 4308 BALI,

4322 LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly  
CTCACCGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAACTGCGGC  
GAGTGGCTCTCCGAAATACAACCCCGGAGAAATGGTTAAGTTCCCCCTCTTGACGCCG

4345 APAI,

4382 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys  
TATCGCAGGTGCCGCGCAGCGGCGTACTGACAACCTAGCTGTGGTAACACCCTCACTGTC  
ATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTGTGGGAGTGAACG

4442 TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal  
TACATCAAGGCGGGCAGCCTGTGAGCCGAGGGCTCCAGGACTGCACCATGCTCGTG  
ATGTAGTTCCGGGCGCGTCCGACAGCTCGGCGTCCCGAGGTCTTGACGTGGTACGAGCAC

4452 SMAI XMAI,

4502 CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer  
TGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGTCCAGGAGGACGCGCGCAGC  
ACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCCTCCTGCGCCGCTCG

4508 DRD1, 4511 TTH3I,

4562 LeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspProProGln  
CTGAGAGCCTTCACGGAGGCTATGACCAGTACTCGCCCCCCTGGGGACCCCCACAA  
GACTCTCGGAAGTGCCTCCGATACTGGTCCATGAGGCGGGGGGACCCCTGGGGGGTGT

4622 ProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAlaHisAsp  
CCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTGAGTCCGCCACGAC  
GGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGGGTGTG

4637 SACI,

4682 GlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAlaArgAla  
GGCGCTGGAAAGAGGGTCTACTACCTACCCGTGACCCTACAACCCCTCGCGAGAGCT  
CCGCGACCTTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGGAGCGCTCTCGA

4731 NRUI,

4742 AlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIleMetPhe  
GCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATCATGTTT  
CGCACCTCTGTGTTCTGTGTGAGGTGAGTTAAGGACCGATCCGTTGTATTAGTACAAA

4802 AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla  
GCCCCACACTGTGGGCGAGGATGATACTGATGACCATTTCTTTAGCGTCTTATAGCC  
CGGGGTGTGACACCCGCTCCTACTATGACTACTGGGTAAAGAAATCGCAGGAATATCGG

4806 PFLM1, 4807 DRA3,

ArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSerIleGlu

4862 AGGGACCAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA.  
TCCCTGGTCTGAACCTGTCCGGGAGCTAACGCTCTAGATGCCCCGGACGATGAGGTATCTT  
4893 BGL2,  
ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis  
4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC  
GGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTCGCGTAAAAGTGAGGTG  
4954 NCOI,  
SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro  
4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAAACCTTGGGGTACCG  
TCAATGAGAGGTCCACTTTAGTTATCCACCGGCGTACGGAGTCTTTTGAACCCCATGGC  
5015 SPHI, 5035 KPNI,  
ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly  
5042 CCCTTGCGAGCTTGGAGACACCGGGCCCGAGCGTCCGCGTAGGCTTCTGGCCAGAGGA  
GGGAACGCTCGAACCTCTGTGGCCCCGGGCTCGCAGGCGCGATCCGAAGACCGGTCTCCT  
5064 APAI, 5091 BALI,  
GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys  
5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCGAGTAAGAACAAAGCTCAA  
CCGTCCCGACGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT  
5113 NDEI,  
LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr  
5162 CTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTACGGCTGGCTAC  
GAGTGAGGTTATCGCCGCGACCGGTGACCTGAACAGGCCGACCAAGTGCCGACCGATG  
5174 NOTI, 5175 EAGI XMA3, 5182 BALI, 5186 PVU2,  
SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys  
5222 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCGGGCCCCGCTGGATCTGGTTTTGC  
TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCCGGGGCGACCTAGACCAAACG  
5240 DRA3,  
LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn  
5282 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCCAACCGAATGAGCACGAAT  
GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTTGGCTTACTCGTGCTTA  
5295 PSTI,  
ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe  
5342 CCTAAACCTCAAAGAAAGACCAACGTAACACCAACCGGCGGCCGAGGACGTCAAGTTC  
GGATTTGGAGTTTCTTTCTGGTTTGATTGTGGTTGGCCGCCGGCGTCTGCAAGTTCAG  
5380 NOTI, 5381 EAGI XMA3, 5390 AAT2, 5401 SMAI XMAI,  
ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu  
5402 CCGGGTGGCGGTGAGTCTGGTGGAGTTTACTTGTGTGCCGCGCAGGGGCCCTAGATTG  
GGCCACCGCCAGTCTAGCAACCACCTCAAATGAACAACGGCGCGTCCCCGGGATCTAA





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MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn  
 2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC  
 TCGAATGTTTTGTTTTACCGACGTATACGTGAGTCCCGATATTCCACGATCATGAGTTG  
 ^ ^ ^  
 1 HIND3, 24 NDEI, 52 SCAI,  
 ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp  
 62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT  
 GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA  
 ^  
 116 CLAI,  
 ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr  
 122 CCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCAGTACTCCACC  
 GGATTGTAGTCTCGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGATGAGGTGG  
 TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys  
 182 TACGGCAAGTTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT  
 ATGCCGTTCAAGGAACGGCTGCCGCCCCACGAGCCCCCGGAATACTGTATTATTAAACA  
 AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln  
 242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA  
 CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAGTGGTT  
 AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal  
 302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC  
 CGTCTCTGACGCCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCAG  
 ^  
 303 ALWN1,  
 ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe  
 362 ACTGTGCCCCATCCCAACATCGAGGAGTTGCTCTGTCCACCACCGGAGAGATCCCTTTT  
 TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA  
 TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis  
 422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTCAT  
 ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA







2342 LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle  
 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC  
 TTCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG  
  
 2402 ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet  
 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCCTAGGACCTGCAGGAACATG  
 TGACCTGTACAGTTTTTGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCCTTGATAC  
 ^ ^ ^  
 2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,  
  
 2462 TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla  
 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCTGTACCCCCCTTCTGCG  
 ACCTCACCTGGAAGGGTAATTACGGATGTGGTGCCCGGGACATGGGGGAAGGACGC  
 ^ ^  
 2480 ASE1, 2497 APAI,  
  
 2522 ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln  
 CCGAACTACACGTTTCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG  
 GGCTTGATGTGCAAGCGGATACCTCCACAGACGTCTCCTTATGCACCTCTATTCCGTC  
 ^  
 2553 PSTI,  
  
 2582 ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln  
 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCGTGCCAG  
 CACCCCTGAAGGTGATGCACTGCCCATACTGATGACTGTTAGAATTTACGGGCACGGTC  
 ^  
 2594 DRA3,  
  
 2642 ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro  
 GTCCCATCGCCGAATTTTTTACAGAATTGGACGGGGTGGCCTACATAGGTTTGGCCCC  
 CAGGGTAGCGGGCTTAAAAAGTGTCTTAACCTGCCCCACGCGGATGTATCAAACGCGGG  
  
 2702 ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro  
 CCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTACAGAGTAGGACTCCACGAATACCCG  
 GGGACGTTGCGGAACGACGCCCTCCTCCATAGTAAGTCTCATCCTGAGGTGCTTATGGGC  
 ^  
 2757 HGIE2,  
  
 2762 ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu  
 GTAGGGTCGCAATTACCTTGCGAGCCCGAACCAGGACGTGGCCGTGTTGACGTCCATGCTC  
 CATCCAGCGTTAATGGAACGCTCGGGCTTGGCCTGCACCGGCACAACTGCAGGTACGAG  
 ^  
 2809 AAT2,  
  
 2822 ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro  
 ACTGATCCCTCCCATATAACAGCAGAGGCGGGCGGCGAAGGTTGGCGAGGGGATCACCC  
 TGACTAGGGAGGGTATATTGTCGTCTCCGCCGGCCCGCTTCCAACCGCTCCCCTAGTGGG  
 ^  
 2850 EAG1 XMA3,  
  
 2882 ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys  
 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC  
 GGGAGACACCGGTGAGGAGCCGATCGGTCGATAGGCGAGGTAGAGAGTTCCGTTGAACG  
 ^ ^  
 2889 BALI, 2903 NHEI,

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2942 ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrpArgGln  
 ACCGCTAACCATGACTCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG  
 TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGTTGGAGGATACCTCCGTC  
 ^ ^  
 2966 ESP1, 2969 SACI,  
 3002 GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer  
 GAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC  
 CTCTACCCGCCGTTGTAGTGGTCCCAACTCAGTCTTTTGTTCACCACTAAGACCTGAGG  
 3062 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu  
 TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGAGATCTCCGTACCCGCAGAAATCCTG  
 AAGCTAGGCGAACACCGCCTCCTCCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC  
 ^  
 3096 BGL2,  
 3122 ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro  
 CGGAAGTCTCGGAGATTCGCCCAGGCCCTGCCGTTTGGGCGCGCCGGACTATAACCCC  
 GCCTTCAGAGCCTTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGCCCTGATATTGGGG  
 ^ ^  
 3143 ALWN1, 3164 EAG1 XMA3,  
 3182 ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro  
 CCGCTAGTGGAGACGTGGAAAAAGCCCCACTACGAACCACCTGTGGTCCATGGCTGCCCCG  
 GGCGATCACCTCTGCACCTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGGC  
 ^ ^  
 3217 HGIE2, 3229 NCOI,  
 3242 LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu  
 CTTCCACCTCCAAAGTCCCCTCCTGTGCCTCCGCCTCGGAAGAAGCGGACGGTGGTCCCTC  
 GAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG  
 3302 ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer  
 ACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC  
 TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG  
 ^ ^  
 3332 SACI, 3346 HIND3,  
 3362 SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly  
 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCGCCCTTCTGGC  
 AGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG  
 3422 CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro  
 TGCCCCCCCCGACTCCGACGCTGAGTCCTATTCTCCATGCCCCCCTGGAGGGGGAGCCT  
 ACGGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA  
 ^  
 3437 EAM11051,  
 3482 GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu  
 GGGGATCCGGATCTTAGCGACGGGTCAATGCTCAACGGTCAGTAGTGAGGCCAACGCGGAG  
 CCCCTAGGCCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGGTTGCGCCTC  
 ^ ^ ^  
 3484 BAMHI, 3485 BSAB1, 3487 BSPE1,  
 3542 AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla  
 GATGTCGTGTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCAACCCGTCGCCG  
 CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCTGAGCAGTGGGGCACGCGG

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# FIGURE 22 - Page 7

3589 DRA3, 3600 SAC2,

3602 AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn  
GCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTCACCACAAT  
CGCCTTCTTGCTTTGACGGGTAGTTACGTGATTCGTTGAGCAACGATGCAGTGGTGTTA

3611 ALWN1, 3655 PFLM1,

3662 LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp  
TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACATTTGAC  
AACCACATAAGGTGGTGGAGTGCCTCACGAACGGTTTCCGTCTTCTTTCAGTGTAACCTG

3681 DRA3,

3722 ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla  
AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGCG  
TCTGACGTTCAAGACCTGTCGGTAATGGTCCTGCATGAGTTCCTCAATTTCTGTCGCCGC

3782 SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis  
TCAAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGACAGCCTGACGCCCCACAC  
AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTCGGACTGCGGGGTGTG

3816 HIND3,

3842 SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla  
TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAAGACGTCCGTTGCCATGCCAGAAAGGCC  
AGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCTTTCCGG

3875 AAT2, 3890 BGLI,

3902 ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp  
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4022 ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu  
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4082 TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr  
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ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAGTTATG

4142 SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet  
TCACCAGGACAGCGGGTTGAATTCCTCGTGCAAGCGTGGAAGTCCAAGAAAACCCCAATG  
AGTGGTCTGTGCGCCCACTTAAGGAGCACGTTTCGCACCTTCAGGTTCTTTGGGGTTAC

4160 ECORI,

4202 GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr  
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4229 DRD1, 4236 ALWN1,

4262 GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer  
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4301 BGLI, 4308 BALI,

4322 LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly  
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4382 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys  
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4442 TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal  
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4452 SMAI XMAI,

4502 CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer  
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4508 DRD1, 4511 TTH3I,

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CGCACCTCTGTCGTTCTGTGTGAGGTCAAGTAAGGACCGATCCGTTGTATTAGTACAAA

4802 AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla  
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4806 PFLM1, 4807 DRA3,

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5064 APAI, 5091 BALI,

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5295 PSTI,

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5380 NOTI, 5381 EAGI XMA3, 5390 AAT2, 5401 SMAI XMAI,

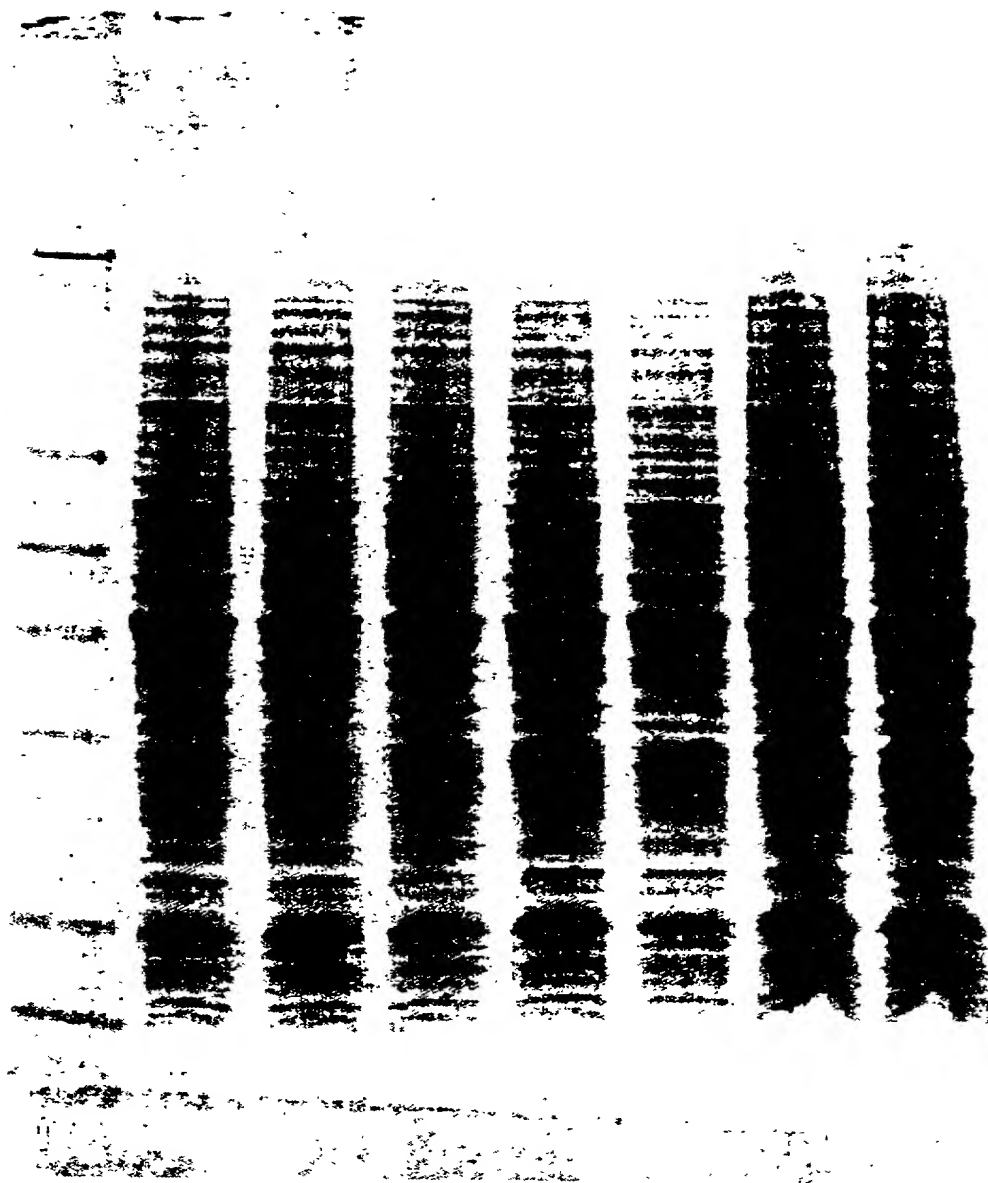
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0024756472650

Variable	Mean	SD	Min	Max
Age	34.5	10.2	18	65
Gender	0.5	0.5	0	1
Marital status	0.6	0.5	0	1
Education	12.5	1.5	9	16
Income	15.2	5.8	5	35
Occupation	1.2	0.8	0	2
Health status	1.5	0.5	1	2
Stress level	2.5	1.2	1	4
Life satisfaction	3.5	1.5	1	5
Resilience	4.5	1.5	1	6
Optimism	3.5	1.5	1	5
Self-efficacy	4.5	1.5	1	6
Emotional stability	3.5	1.5	1	5
Prosocial behavior	3.5	1.5	1	5
Empathy	3.5	1.5	1	5
Agreeableness	3.5	1.5	1	5
Conscientiousness	3.5	1.5	1	5
Neuroticism	3.5	1.5	1	5
Openness	3.5	1.5	1	5
Extraversion	3.5	1.5	1	5
Intelligence	100	15	70	130
Memory	85	10	60	110
Attention	75	10	50	100
Processing speed	90	10	60	120
Verbal ability	80	10	50	110
Nonverbal ability	85	10	50	120
Fluid intelligence	90	10	60	120
Crystalline intelligence	85	10	50	120
Executive function	80	10	50	110
Working memory	75	10	50	100
Inhibition	70	10	40	100
Planning	75	10	40	100
Flexibility	70	10	40	100
Problem solving	75	10	40	100
Decision making	70	10	40	100
Emotional regulation	75	10	40	100
Stress management	70	10	40	100
Resilience	75	10	40	100
Optimism	70	10	40	100
Self-efficacy	75	10	40	100
Emotional stability	70	10	40	100
Prosocial behavior	75	10	40	100
Empathy	70	10	40	100
Agreeableness	75	10	40	100
Conscientiousness	70	10	40	100
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Extraversion	75	10	40	100
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Memory	85	10	60	110
Attention	75	10	50	100
Processing speed	90	10	60	120
Verbal ability	80	10	50	110
Nonverbal ability	85	10	50	120
Fluid intelligence	90	10	60	120
Crystalline intelligence	85	10	50	120
Executive function	80	10	50	110
Working memory	75	10	50	100
Inhibition	70	10	40	100
Planning	75	10	40	100
Flexibility	70	10	40	100
Problem solving	75	10	40	100
Decision making	70	10	40	100
Emotional regulation	75	10	40	100
Stress management	70	10	40	100
Resilience	75	10	40	100
Optimism	70	10	40	100
Self-efficacy	75	10	40	100
Emotional stability	70	10	40	100
Prosocial behavior	75	10	40	100
Empathy	70	10	40	100
Agreeableness	75	10	40	100
Conscientiousness	70	10	40	100
Neuroticism	75	10	40	100
Openness	70	10	40	100
Extraversion	75	10	40	100

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 5462 GGTGTGCGCGCGACGAGAAAGACTTCCGAGCGGTGCGAACCTCGAGGTAGACGTCAGCCT  
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 5467 BSSH2, 5478 XMNI, 5502 XHOI, 5511 AAT2,  
  
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 5650 APAI, 5696 CLAI,  
  
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 5724 HGIE2, 5750 KAS1 NARI, 5756 ECON1,  
  
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 5762 GGAGGCGCTGCCAGGGCCTAATAGTCGAC  
 CCTCCGCGACGGTCCCGGATTATCAGCTG  
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 5785 SALI,

FIGURE 23



002211 524250

COMBINED DECLARATION AND POWER OF ATTORNEY  
FOR UTILITY PATENT APPLICATION

AS A BELOW-NAMED INVENTOR, I HEREBY DECLARE THAT:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: NOVEL HCV NON-STRUCTURAL POLYPEPTIDE the specification of which

  X   is attached hereto  
       was filed on

and assigned Serial No.

I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE.

I acknowledge and understand that I am an individual who has a duty to disclose information which is material to the patentability of the claims of this application in accordance with Title 37, Code of Federal Regulations, §§ 1.56(a) and (b) which state:

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated

through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office,

or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

I do not know and do not believe this invention was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to said application. This invention was not in public use or on sale in the United States of America more than one year prior to this application. This invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on any application filed by me or my legal representatives or assigns more than six months prior to this application.

I hereby claim priority benefits under Title 35, United States Code § 119(e)(1) of any United States provisional application(s) for patent as indicated below and have also identified below any application for patent on this invention having a filing date before that of the application for patent on which priority is claimed:

<u>Application No.</u>	<u>Date of Filing (day/month/year)</u>	<u>Priority Claimed</u>
60/167,502	24 November 1999	Yes <u>X</u> No <u>  </u>

I hereby appoint the following attorneys and agents to prosecute that application and to transact all business in the Patent and Trademark Office connected therewith and to file, to prosecute and to transact all business in connection with all patent applications directed to the invention:

Lisa E. Alexander, Reg. No. 41,576  
Robert P. Blackburn, Reg. No. 30,447  
Anne S. Dollard, Reg. No. 43,935  
Joseph H. Guth, Reg. No. 31,261  
Alisa A. Harbin, Reg. No. 33,895  
Charlene A. Launer, Reg. No. 33,035  
David P. Lentini, Reg. No. 33,944  
Kimberlin L. Morley, Reg. No. 35,391  
Roberta L. Robins, Reg. No. 33,208  
Dahna S. Pasternak, Reg. No. 41,411  
Gary R. Fabian, Ph.D., Reg. No. 33,875  
Cathleen M. Rocco, Reg. No. 46,172

Address all correspondence to: Alisa A. Harbin at

CHIRON CORPORATION  
Intellectual Property - R440  
P.O. Box 8097  
Emeryville, CA 94662-8097.

Address all telephone calls to: Alisa A. Harbin at (510) 923-2708.

This appointment, including the right to delegate this appointment, shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signature: \_\_\_\_\_

Date \_\_\_\_\_

Full Name of Inventor: Doris COIT

Citizenship: US

Residence:

Post Office Address: c/o Chiron Corporation, 4560 Horton Street - R440, Emeryville, CA 94608

Signature: \_\_\_\_\_

Date \_\_\_\_\_

Full Name of Inventor: Angelica MEDINA-SELBY

Citizenship: US

Residence: San Francisco, CA

Post Office Address: c/o Chiron Corporation, 4560 Horton Street - R440, Emeryville, CA 94608

Signature: \_\_\_\_\_

Date \_\_\_\_\_

Full Name of Inventor: Mark SELBY

Citizenship: US

Residence: San Francisco, CA

Post Office Address: c/o Chiron Corporation, 4560 Horton Street - R440, Emeryville, CA 94608

Signature: \_\_\_\_\_

Date \_\_\_\_\_

Full Name of Inventor: Michael HOUGHTON

Citizenship: UK

Residence: Berkeley, CA

Post Office Address: c/o Chiron Corporation, 4560 Horton Street - R440, Emeryville, CA 94608

002217-647260



Atty Dkt No. PP01617.002  
PATENT

"Express Mail" Mailing Label No. EL 668 933 832 US  
Date of Deposit November 22, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

PATRICIA K. HIMONES  
Typed or Printed Name of Person Mailing Paper or Fee

Patricia K. Himones  
Signature of Person Mailing Paper or Fee

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

COIT et al.

Serial No.:

Group Art Unit: Unassigned

Filing Date: even date

Examiner: Unassigned

Title: NOVEL HCV NON-STRUCTURAL POLYPEPTIDE

STATEMENT TO SUPPORT FILING AND SUBMISSION IN ACCORDANCE  
WITH 37 C.F.R. §§ 1.821-1.825

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

The undersigned hereby states that the content of the attached papers and the computer-readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. §§ 1.821(c) and (e), respectively, are the same.

Respectfully submitted,

Date: Nov 22, 2000

By: D. Pasternak  
Dahna S. Pasternak  
Registration No. 41,411  
Attorney for Applicants

CHIRON CORPORATION  
Intellectual Property - R440  
P.O. Box 8097  
Emeryville, CA 94662-8097  
Telephone: (510) 923-2708

Facsimile: (510) 655-3542

002231 544260

# SEQUENCE LISTING

<110> Coit, Doris  
Medina-Selby, Angelica  
Selby, Mark  
Houghton, Michael

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 gaattcacc atg gct gca tat gca gct cag ggc tat aag gtg cta gta ctc 2031  
 Met Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu  
 1 5 10  
 aac ccc tct gtt gct gca aca ctg ggc ttt ggt gct tac atg tcc aag 2079  
 Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys  
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 Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr  
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 act ggc agc ccc atc acg tac tcc acc tac ggc aag ttc ctt gcc gac 2175  
 Thr Gly Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp  
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Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro	
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Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr	
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Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly	
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Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val	
575 580 585 590	
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Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys	
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Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala	
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Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp	
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ctg gtc aat cta ctg ccc gcc atc ctc tcg ccc gga gcc ctc gta gtc	3951
Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val	
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Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu	
655 660 665 670	
ggg gca gtg cag tgg atg aac cgg ctg ata gcc ttc gcc tcc cgg ggg	4047
Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly	
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Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala	
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Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg	
705 710 715	
cga ctg cac cag tgg ata agc tcg gag tgt acc act cca tgc tcc ggt	4191
Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly	
720 725 730	
tcc tgg cta agg gac atc tgg gac tgg ata tgc gag gtg ttg agc gac	4239
Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp	
735 740 745 750	
ttt aag acc tgg cta aaa gct aag ctc atg cca cag ctg cct ggg atc	4287

Phe	Lys	Thr	Trp	Leu	Lys	Ala	Lys	Leu	Met	Pro	Gln	Leu	Pro	Gly	Ile		
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ccc	ttt	gtg	tcc	tgc	cag	cgc	ggg	tat	aag	ggg	gtc	tgg	cga	ggg	gac	4335	
Pro	Phe	Val	Ser	Cys	Gln	Arg	Gly	Tyr	Lys	Gly	Val	Trp	Arg	Gly	Asp		
			770					775					780				
ggc	atc	atg	cac	act	cgc	tgc	cac	tgt	gga	gct	gag	atc	act	gga	cat	4383	
Gly	Ile	Met	His	Thr	Arg	Cys	His	Cys	Gly	Ala	Glu	Ile	Thr	Gly	His		
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Val	Lys	Asn	Gly	Thr	Met	Arg	Ile	Val	Gly	Pro	Arg	Thr	Cys	Arg	Asn		
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Thr	Pro	Leu	Pro	Ala	Pro	Asn	Tyr	Thr	Phe	Ala	Leu	Trp	Arg	Val	Ser		
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gca	gag	gaa	tac	gtg	gag	ata	agg	cag	gtg	ggg	gac	ttc	cac	tac	gtg	4575	
Ala	Glu	Glu	Tyr	Val	Glu	Ile	Arg	Gln	Val	Gly	Asp	Phe	His	Tyr	Val		
			850					855					860				
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Thr	Gly	Met	Thr	Thr	Asp	Asn	Leu	Lys	Cys	Pro	Cys	Gln	Val	Pro	Ser		
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ccc	gaa	ttt	ttc	aca	gaa	ttg	gac	ggg	gtg	cgc	cta	cat	agg	ttt	gcg	4671	
Pro	Glu	Phe	Phe	Thr	Glu	Leu	Asp	Gly	Val	Arg	Leu	His	Arg	Phe	Ala		
	880					885					890						
ccc	ccc	tgc	aag	ccc	ttg	ctg	cgg	gag	gag	gta	tca	ttc	aga	gta	gga	4719	
Pro	Pro	Cys	Lys	Pro	Leu	Leu	Arg	Glu	Glu	Val	Ser	Phe	Arg	Val	Gly		
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ctc	cac	gaa	tac	ccg	gta	ggg	tcg	caa	tta	cct	tgc	gag	ccc	gaa	ccg	4767	
Leu	His	Glu	Tyr	Pro	Val	Gly	Ser	Gln	Leu	Pro	Cys	Glu	Pro	Glu	Pro		
				915					920					925			
gac	gtg	gcc	gtg	ttg	acg	tcc	atg	ctc	act	gat	ccc	tcc	cat	ata	aca	4815	
Asp	Val	Ala	Val	Leu	Thr	Ser	Met	Leu	Thr	Asp	Pro	Ser	His	Ile	Thr		
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gca	gag	gcg	gcc	ggg	cga	agg	ttg	gcg	agg	gga	tca	ccc	ccc	tct	gtg	4863	
Ala	Glu	Ala	Ala	Gly	Arg	Arg	Leu	Ala	Arg	Gly	Ser	Pro	Pro	Ser	Val		
		945					950					955					
gcc	agc	tcc	tcg	gct	agc	cag	cta	tcc	gct	cca	tct	ctc	aag	gca	act	4911	
Ala	Ser	Ser	Ser	Ala	Ser	Gln	Leu	Ser	Ala	Pro	Ser	Leu	Lys	Ala	Thr		
	960					965					970						
tgc	acc	gct	aac	cat	gac	tcc	cct	gat	gct	gag	ctc	ata	gag	gcc	aac	4959	
Cys	Thr	Ala	Asn	His	Asp	Ser	Pro	Asp	Ala	Glu	Leu	Ile	Glu	Ala	Asn		







Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys	
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Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly	
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Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala	
	1475 1480 1485
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Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val	
	1490 1495 1500
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Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala	
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Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro	
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Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val	
	1535 1540 1545 1550
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Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg	
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Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His	
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act cca gtc aat tcc tgg cta ggc aac ata atc atg ttt gcc ccc aca	6783
Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe Ala Pro Thr	
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ctg tgg gcg agg atg ata ctg atg acc cat ttc ttt agc gtc ctt ata	6831
Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Val Leu Ile	
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gcc agg gac cag ctt gaa cag gcc ctc gat tgc gag atc tac ggg gcc	6879
Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile Tyr Gly Ala	
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tgc tac tcc ata gaa cca ctg gat cta cct cca atc att caa aga ctc	6927
Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu	
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cat ggc ctc agc gca ttt tca ctc cac agt tac tct cca ggt gaa atc	6975
His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile	
	1650 1655 1660
aat agg gtg gcc gca tgc ctc aga aaa ctt ggg gta ccg ccc ttg cga	7023
Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg	

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1665	1670	1675	
gct tgg aga cac cgg gcc cgg agc gtc cgc gct agg ctt ctg gcc aga			7071
Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg			
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gga ggc agg gct gcc ata tgt ggc aag tac ctc ttc aac tgg gca gta			7119
Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val			
1695	1700	1705	1710
aga aca aag ctc aaa ctc act cca ata gcg gcc gct ggc cag ctg gac			7167
Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp			
1715	1720	1725	
ttg tcc ggc tgg ttc acg gct ggc tac agc ggg gga gac att tat cac			7215
Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His			
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agc gtg tct cat gcc cgg ccc cgc tgg atc tgg ttt tgc cta ctc ctg			7263
Ser Val Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu			
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Leu Ala Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg			
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gccactggta acaggattag cagagcgagg tatgtaggcg gtgctacaga gttcttgaag			8212
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1	5	10	15
Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His	20	25	30
Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly	35	40	45
Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly	50	55	60
Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser	65	70	75
Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala	85	90	95
Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro	100	105	110
Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser	115	120	125
Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val	130	135	140
Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys	145	150	155
Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala	165	170	175
Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val	180	185	190
Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe	195	200	205
Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe	210	215	220
Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp	225	230	235
Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro	245	250	255
Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe	260	265	270
Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr	275	280	285
Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn	290	295	300
Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly			

305	310	315	320
Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr	325	330	335
Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr	340	345	350
Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp	355	360	365
Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu	370	375	380
Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile Thr Leu Thr His Pro	385	390	395
Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val	405	410	415
Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala	420	425	430
Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val Gly Arg Val Val Leu	435	440	445
Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu	450	455	460
Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln	465	470	475
Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu	485	490	495
Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val Gln Thr	500	505	510
Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys His Met Trp Asn Phe	515	520	525
Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn	530	535	540
Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro	545	550	555
Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val	565	570	575
Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala	580	585	590
Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu	595	600	605
Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val			



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Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu														
930					935					940				
Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Val Ala Ser					950				955				960	
945														
Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr					965				970				975	
Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn Leu Leu					980				985				990	
Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn														
995									1000				1005	
Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu Val Ala Glu Glu Asp														
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Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Arg Arg														
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													1040	
Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro Asp Tyr Asn Pro Pro														
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Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu Pro Pro Val Val His														
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Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro Val Pro Pro Pro Arg														
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Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr Leu Ser Thr Ala Leu														
1090									1095				1100	
Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser Ser Thr Ser Gly Ile														
105									1110				1115	
													1120	
Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys														
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Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu														
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Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val														
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Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys Cys Ser Met Ser Tyr														
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Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys														
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Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu														
1205									1210				1215	
Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys Lys Val														



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Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu		
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Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser		
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Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys		
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Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val		
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Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr		
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Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln		
1315	1320	1325
Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp		
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Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr		
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Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser		
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Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys		
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Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val		
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Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp		
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Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu		
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Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr		
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Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr		
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Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu		
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Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys		
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Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala Phe Thr		
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Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Gln Pro		

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Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro		
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Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro		
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Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe Ala Pro Thr Leu Trp		
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Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Val Leu Ile Ala Arg		
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Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile Tyr Gly Ala Cys Tyr		
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Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly		
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Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg		
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Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp		
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Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg Gly Gly		
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Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr		
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Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp Leu Ser		
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Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val		
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<220>  
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<220>

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His	Pro	Val	Thr	Lys	Tyr	Ile	Met	Thr	Cys	Met	Ser	Ala	Asp	Leu	Glu	



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Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser  
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85 90 95  
Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro  
100 105 110  
Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser  
115 120 125  
Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val  
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Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys  
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Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala  
165 170 175



Gly	Met	Met	Leu	Ala	Glu	Gln	Phe	Lys	Gln	Lys	Ala	Leu	Gly	Leu	Leu	485	490	495
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Asn	Trp	Gln	Lys	Leu	Glu	Thr	Phe	Trp	Ala	Lys	His	Met	Trp	Asn	Phe	515	520	525
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Pro	Ala	Ile	Ala	Ser	Leu	Met	Ala	Phe	Thr	Ala	Ala	Val	Thr	Ser	Pro	545	550	555
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Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys  
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Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser  
 1365 1370 1375

Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys  
 1380 1385 1390



Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr  
 1700 1705 1710

Lys Leu Lys Leu Thr Pro Ile Ala Ala Gly Gln Leu Asp Leu Ser  
 1715 1720 1725

Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val  
 1730 1735 1740

Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu Leu Ala  
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Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg  
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<211> 4282

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: pCMVII

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<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: pNS34a

<220>  
<221> CDS  
<222> (1990)..(4047)

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ccattactaa tccataacat ggctctttgc cacaactatc tctattgggt atatgccaat 1380

Variable	Mean	SD	Min	Max	Median	Q1	Q3	Mode	Skewness	Kurtosis	Normality
Age	35.2	12.5	18	65	32	28	38	35	0.15	3.2	0.95
Gender	1.2	0.4	1	2	1	1	2	1	-0.1	1.5	0.98
Marital Status	2.1	0.8	1	3	2	1	3	2	0.2	2.1	0.92
Education	15.8	2.5	10	20	16	15	17	16	-0.05	2.8	0.97
Income	1200	300	500	2000	1100	900	1300	1000	0.1	3.5	0.94
Occupation	1.5	0.5	1	3	2	1	3	2	-0.1	1.8	0.96
Health Status	2.5	0.5	1	3	2	2	3	2	-0.1	1.5	0.98
Stress Level	3.2	1.0	1	5	3	2	4	3	0.1	2.5	0.93
Life Satisfaction	4.5	0.8	3	5	4	4	5	4	-0.1	1.2	0.99
Resilience	3.8	0.9	2	5	4	3	5	4	-0.1	1.8	0.96
Optimism	4.2	0.7	3	5	4	4	5	4	-0.1	1.0	0.99
Gratitude	4.8	0.6	3	5	4	4	5	4	-0.1	0.8	0.99
Forgiveness	4.6	0.7	3	5	4	4	5	4	-0.1	1.0	0.99
Empathy	4.4	0.8	3	5	4	4	5	4	-0.1	1.2	0.98
Self-Compassion	4.3	0.9	3	5	4	4	5	4	-0.1	1.5	0.97
Emotional Stability	4.1	0.7	3	5	4	4	5	4	-0.1	1.0	0.99
Psychological Well-being	4.0	0.8	3	5	4	4	5	4	-0.1	1.2	0.98
Life Purpose	3.9	0.9	2	5	4	3	5	4	-0.1	1.8	0.96
Meaning in Life	3.7	0.8	2	5	4	3	5	4	-0.1	1.5	0.97
Existential Well-being	3.6	0.9	2	5	4	3	5	4	-0.1	1.8	0.96
Transcendental Well-being	3.5	0.8	2	5	4	3	5	4	-0.1	1.5	0.97
Overall Well-being	3.4	0.9	2	5	4	3	5	4	-0.1	1.8	0.96

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Val	Cys	Thr	Arg	Gly	Val	Ala	Lys	Ala	Val	Asp	Phe	Ile	Pro	Val	Glu	
	160					165					170					
aac	cta	gag	aca	acc	atg	agg	tcc	ccg	gtg	ttc	acg	gat	aac	tcc	tct	2559
Asn	Leu	Glu	Thr	Thr	Met	Arg	Ser	Pro	Val	Phe	Thr	Asp	Asn	Ser	Ser	
175					180					185					190	
cca	cca	gta	gtg	ccc	cag	agc	ttc	cag	gtg	gct	cac	ctc	cat	gct	ccc	2607
Pro	Pro	Val	Val	Pro	Gln	Ser	Phe	Gln	Val	Ala	His	Leu	His	Ala	Pro	
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aca	ggc	agc	ggc	aaa	agc	acc	aag	gtc	ccg	gct	gca	tat	gca	gct	cag	2655
Thr	Gly	Ser	Gly	Lys	Ser	Thr	Lys	Val	Pro	Ala	Ala	Tyr	Ala	Ala	Gln	
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Phe	Gly	Ala	Tyr	Met	Ser	Lys	Ala	His	Gly	Ile	Asp	Pro	Asn	Ile	Arg	
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acc	ggg	gtg	aga	aca	att	acc	act	ggc	agc	ccc	atc	acg	tac	tcc	acc	2799
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tac	ggc	aag	ttc	ctt	gcc	gac	ggc	ggg	tgc	tcg	ggg	ggc	gct	tat	gac	2847
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ata	ata	att	tgt	gac	gag	tgc	cac	tcc	acg	gat	gcc	aca	tcc	atc	ttg	2895
Ile	Ile	Ile	Cys	Asp	Glu	Cys	His	Ser	Thr	Asp	Ala	Thr	Ser	Ile	Leu	
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ggc	att	ggc	act	gtc	ctt	gac	caa	gca	gag	act	gcg	ggg	gcg	aga	ctg	2943
Gly	Ile	Gly	Thr	Val	Leu	Asp	Gln	Ala	Glu	Thr	Ala	Gly	Ala	Arg	Leu	
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Val	Val	Leu	Ala	Thr	Ala	Thr	Pro	Pro	Gly	Ser	Val	Thr	Val	Pro	His	
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ccc	aac	atc	gag	gag	gtt	gct	ctg	tcc	acc	acc	gga	gag	atc	cct	ttt	3039
Pro	Asn	Ile	Glu	Glu	Val	Ala	Leu	Ser	Thr	Thr	Gly	Glu	Ile	Pro	Phe	
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tac	ggc	aag	gct	atc	ccc	ctc	gaa	gta	atc	aag	ggg	ggg	aga	cat	ctc	3087
Tyr	Gly	Lys	Ala	Ile	Pro	Leu	Glu	Val								







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<211> 686

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: pNS34a

<400> 7

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			20					25					30		
Glu	Val	Gln	Ile	Val	Ser	Thr	Ala	Ala	Gln	Thr	Phe	Leu	Ala	Thr	Cys
		35					40					45			

Ile	Asn	Gly	Val	Cys	Trp	Thr	Val	Tyr	His	Gly	Ala	Gly	Thr	Arg	Thr	50	55	60	
Ile	Ala	Ser	Pro	Lys	Gly	Pro	Val	Ile	Gln	Met	Tyr	Thr	Asn	Val	Asp	65	70	75	80
Gln	Asp	Leu	Val	Gly	Trp	Pro	Ala	Ser	Gln	Gly	Thr	Arg	Ser	Leu	Thr	85	90	95	
Pro	Cys	Thr	Cys	Gly	Ser	Ser	Asp	Leu	Tyr	Leu	Val	Thr	Arg	His	Ala	100	105	110	
Asp	Val	Ile	Pro	Val	Arg	Arg	Arg	Gly	Asp	Ser	Arg	Gly	Ser	Leu	Leu	115	120	125	
Ser	Pro	Arg	Pro	Ile	Ser	Tyr	Leu	Lys	Gly	Ser	Ser	Gly	Gly	Pro	Leu	130	135	140	
Leu	Cys	Pro	Ala	Gly	His	Ala	Val	Gly	Ile	Phe	Arg	Ala	Ala	Val	Cys	145	150	155	160
Thr	Arg	Gly	Val	Ala	Lys	Ala	Val	Asp	Phe	Ile	Pro	Val	Glu	Asn	Leu	165	170	175	
Glu	Thr	Thr	Met	Arg	Ser	Pro	Val	Phe	Thr	Asp	Asn	Ser	Ser	Pro	Pro	180	185	190	
Val	Val	Pro	Gln	Ser	Phe	Gln	Val	Ala	His	Leu	His	Ala	Pro	Thr	Gly	195	200	205	
Ser	Gly	Lys	Ser	Thr	Lys	Val	Pro	Ala	Ala	Tyr	Ala	Ala	Gln	Gly	Tyr	210	215	220	
Lys	Val	Leu	Val	Leu	Asn	Pro	Ser	Val	Ala	Ala	Thr	Leu	Gly	Phe	Gly	225	230	235	240
Ala	Tyr	Met	Ser	Lys	Ala	His	Gly	Ile	Asp	Pro	Asn	Ile	Arg	Thr	Gly	245	250	255	
Val	Arg	Thr	Ile	Thr	Thr	Gly	Ser	Pro	Ile	Thr	Tyr	Ser	Thr	Tyr	Gly	260	265	270	
Lys	Phe	Leu	Ala	Asp	Gly	Gly	Cys	Ser	Gly	Gly	Ala	Tyr	Asp	Ile	Ile	275	280	285	
Ile	Cys	Asp	Glu	Cys	His	Ser	Thr	Asp	Ala	Thr	Ser	Ile	Leu	Gly	Ile	290	295	300	
Gly	Thr	Val	Leu	Asp	Gln	Ala	Glu	Thr	Ala	Gly	Ala	Arg	Leu	Val	Val	305	310	315	320
Leu	Ala	Thr	Ala	Thr	Pro	Pro	Gly	Ser	Val	Thr	Val	Pro	His	Pro	Asn	325	330	335	
Ile	Glu	Glu	Val	Ala	Leu	Ser	Thr	Thr	Gly	Glu	Ile	Pro	Phe	Tyr	Gly	340	345	350	



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Arg Glu Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys  
675 680 685

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<212> DNA  
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<220>  
<223> Description of Artificial Sequence: pd.deltaNS3NS5

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Val Pro Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala  
1675 1680 1685

agg ctt ctg gcc aga gga ggc agg gct gcc ata tgt ggc aag tac ctc 17859  
Arg Leu Leu Ala Arg Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu  
1690 1695 1700 1705

ttc aac tgg gca gta aga aca aag ctc aaa ctc act cca ata gcg gcc 17907  
Phe Asn Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala  
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gct ggc cag ctg gac ttg tcc ggc tgg ttc acg gct ggc tac agc ggg 17955  
Ala Gly Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly  
1725 1730 1735

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Gly Asp Ile Tyr His Ser Val Ser His Ala Arg Pro Arg Trp Ile Trp  
1740 1745 1750

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1770

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Val	Ser	Pro	Thr	His	Tyr	Val	Pro	Glu	Ser	Asp	Ala	Ala	Ala	Arg	Val	690	695	700	
Thr	Ala	Ile	Leu	Ser	Ser	Leu	Thr	Val	Thr	Gln	Leu	Leu	Arg	Arg	Leu	705	710	715	720
His	Gln	Trp	Ile	Ser	Ser	Glu	Cys	Thr	Thr	Pro	Cys	Ser	Gly	Ser	Trp	725	730	735	
Leu	Arg	Asp	Ile	Trp	Asp	Trp	Ile	Cys	Glu	Val	Leu	Ser	Asp	Phe	Lys	740	745	750	
Thr	Trp	Leu	Lys	Ala	Lys	Leu	Met	Pro	Gln	Leu	Pro	Gly	Ile	Pro	Phe	755	760	765	
Val	Ser	Cys	Gln	Arg	Gly	Tyr	Lys	Gly	Val	Trp	Arg	Gly	Asp	Gly	Ile	770	775	780	
Met	His	Thr	Arg	Cys	His	Cys	Gly	Ala	Glu	Ile	Thr	Gly	His	Val	Lys	785	790	795	800
Asn	Gly	Thr	Met	Arg	Ile	Val	Gly	Pro	Arg	Thr	Cys	Arg	Asn	Met	Trp	805	810	815	
Ser	Gly	Thr	Phe	Pro	Ile	Asn	Ala	Tyr	Thr	Thr	Gly	Pro	Cys	Thr	Pro	820	825	830	
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Glu	Tyr	Val	Glu	Ile	Arg	Gln	Val	Gly	Asp	Phe	His	Tyr	Val	Thr	Gly	850	855	860	
Met	Thr	Thr	Asp	Asn	Leu	Lys	Cys	Pro	Cys	Gln	Val	Pro	Ser	Pro	Glu	865	870	875	880
Phe	Phe	Thr	Glu	Leu	Asp	Gly	Val	Arg	Leu	His	Arg	Phe	Ala	Pro	Pro	885	890	895	
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Ala	Val	Leu	Thr	Ser	Met	Leu	Thr	Asp	Pro	Ser	His	Ile	Thr	Ala	Glu	930	935	940	
Ala	Ala	Gly	Arg	Arg	Leu	Ala	Arg	Gly	Ser	Pro	Pro	Ser	Val	Ala	Ser	945	950	955	960
Ser	Ser	Ala	Ser	Gln	Leu	Ser	Ala	Pro	Ser	Leu	Lys	Ala	Thr	Cys	Thr	965	970	975	
Ala	Asn	His	Asp	Ser	Pro	Asp	Ala	Glu	Leu	Ile	Glu	Ala	Asn	Leu	Leu	980	985	990	



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Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln  
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Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp  
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Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys  
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Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe Ala Pro Thr Leu Trp  
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Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr	
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Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile	
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Thr Leu Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr	
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Gly Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg	
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Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala	
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Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu	
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Arg Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu	
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Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His	
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Phe Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val	
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Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser	
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Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His	
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Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile	
380 385 390 395	
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Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala	
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Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu	
415 420 425	
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ccg ggc gag ggg gca gtg cag tgg atg aac cgg ctg ata gcc ttc gcc			14727
Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala			
670	675	680	
tcc cgg ggg aac cat gtt tcc ccc acg cac tac gtg ccg gag agc gat			14775
Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp			
685	690	695	
gca gct gcc cgc gtc act gcc ata ctc agc agc ctc act gta acc cag			14823
Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln			
700	705	710	715
ctc ctg agg cga ctg cac cag tgg ata agc tcg gag tgt acc act cca			14871
Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro			
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Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val			
735	740	745	
ttg agc gac ttt aag acc tgg cta aaa gct aag ctc atg cca cag ctg			14967
Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu			
750	755	760	
cct ggg atc ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg gtc tgg			15015
Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp			
765	770	775	
cga ggg gac ggc atc atg cac act cgc tgc cac tgt gga gct gag atc			15063
Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile			
780	785	790	795
act gga cat gtc aaa aac ggg acg atg agg atc gtc ggt cct agg acc			15111
Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr			
800	805	810	
tgc agg aac atg tgg agt ggg acc ttc ccc att aat gcc tac acc acg			15159
Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr			
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Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp			
830	835	840	
agg gtg tct gca gag gaa tac gtg gag ata agg cag gtg ggg gac ttc			15255
Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe			
845	850	855	
cac tac gtg acg ggt atg act act gac aat ctt aaa tgc ccg tgc cag			15303
His Tyr Val Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln			
860	865	870	875
gtc cca tcg ccc gaa ttt ttc aca gaa ttg gac ggg gtg cgc cta cat			15351
Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His			
880	885	890	







1340	1345	1350	1355	
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Tyr Asp Val Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr				
1360	1365	1370		
gga ttc caa tac tca cca gga cag cgg gtt gaa ttc ctc gtg caa gcg				16839
Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala				
1375	1380	1385		
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Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys				
1390	1395	1400		
ttt gac tcc aca gtc act gag agc gac atc cgt acg gag gag gca atc				16935
Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile				
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Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser				
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Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly				
1440	1445	1450		
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Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr				
1455	1460	1465		
agc tgt ggt aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt				17127
Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys				
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cga gcc gca ggg ctc cag gac tgc acc atg ctc gtg tgt ggc gac gac				17175
Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp				
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Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser				
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ctg aga gcc ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg				17271
Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly				
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gac ccc cca caa cca gaa tac gac ttg gag ctc ata aca tca tgc tcc				17319
Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser				
1535	1540	1545		
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Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr				
1565	1570	1575		

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Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe  
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Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser  
1600 1605 1610

gtc ctt ata gcc agg gac cag ctt gaa cag gcc ctc gat tgc gag atc 17559  
Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile  
1615 1620 1625

tac ggg gcc tgc tac tcc ata gaa cca ctg gat cta cct cca atc att 17607  
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Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro  
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1695 1700 1705

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1710 1715 1720

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Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp  
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<220>

<223> Description of Artificial Sequence:

pd.deltaNS3NS5.pj

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35 40 45  
Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly  
50 55 60  
Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser  
65 70 75 80  
Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala  
85 90 95  
Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro  
100 105 110  
Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser  
115 120 125  
Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val  
130 135 140  
Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys  
145 150 155 160  
Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala  
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Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val  
180 185 190  
Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe  
195 200 205  
Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe  
210 215 220  
Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp  
225 230 235 240  
Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro  
245 250 255  
Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe  
260 265 270  
Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr

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Thr	Pro	Gly	Leu	Pro	Val	Cys	Gln	Asp	His	Leu	Glu	Phe	Trp	Glu	Gly	
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Val	Phe	Thr	Gly	Leu	Thr	His	Ile	Asp	Ala	His	Phe	Leu	Ser	Gln	Thr	
325					330					335						
Lys	Gln	Ser	Gly	Glu	Asn	Leu	Pro	Tyr	Leu	Val	Ala	Tyr	Gln	Ala	Thr	
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Val	Cys	Ala	Arg	Ala	Gln	Ala	Pro	Pro	Pro	Ser	Trp	Asp	Gln	Met	Trp	
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Lys	Cys	Leu	Ile	Arg	Leu	Lys	Pro	Thr	Leu	His	Gly	Pro	Thr	Pro	Leu	
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Thr	Ser	Thr	Trp	Val	Leu	Val	Gly	Gly	Val	Leu	Ala	Ala	Leu	Ala	Ala	
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Tyr	Cys	Leu	Ser	Thr	Gly	Cys	Val	Val	Ile	Val	Gly	Arg	Val	Val	Leu	
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Ser	Gly	Lys	Pro	Ala	Ile	Ile	Pro	Asp	Arg	Glu	Val	Leu	Tyr	Arg	Glu	
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Phe	Asp	Glu	Met	Glu	Glu	Cys	Ser	Gln	His	Leu	Pro	Tyr	Ile	Glu	Gln	
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Asn	Trp	Gln	Lys	Leu	Glu	Thr	Phe	Trp	Ala	Lys	His	Met	Trp	Asn	Phe	
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Pro	Ala	Ile	Ala	Ser	Leu	Met	Ala	Phe	Thr	Ala	Ala	Val	Thr	Ser	Pro	
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Leu	Thr	Thr	Ser	Gln	Thr	Leu	Leu	Phe	Asn	Ile	Leu	Gly	Gly	Trp	Val	
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Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val		
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Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val		
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Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val		
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Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala		
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Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His		
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Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val		
	690	695
Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu		
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His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp		
	725	730
Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys		
	740	745
Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe		
	755	760
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	770	775
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785	790	795
Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp		
	805	810
Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro		
	820	825
Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp Arg Val Ser Ala Glu		
	835	840
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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:  
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<220>

<221> CDS

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Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val			
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ggc agg gtc gtc ttg tcc ggg aag ccg gca atc ata cct gac agg gaa			14055
Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu			
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gtc ctc tac cga gag ttc gat gag atg gaa gag tgc tct cag cac tta			14103
Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Cys Ser Gln His Leu			
460	465	470	475
ccg tac atc gag caa ggg atg atg ctc gcc gag cag ttc aag cag aag			14151
Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys			
480	485	490	
gcc ctc ggc ctc ctg cag acc gcg tcc cgt cag gca gag gtt atc gcc			14199
Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala			
495	500	505	
cct gct gtc cag acc aac tgg caa aaa ctc gag acc ttc tgg gcg aag			14247
Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys			
510	515	520	
cat atg tgg aac ttc atc agt ggg ata caa tac ttg gcg ggc ttg tca			14295
His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser			
525	530	535	
acg ctg cct ggt aac ccc gcc att gct tca ttg atg gct ttt aca gct			14343
Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala			
540	545	550	555
gct gtc acc agc cca cta acc act agc caa acc ctc ctc ttc aac ata			14391
Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile			
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Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr	
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Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly	
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Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val	
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Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser	
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Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala	
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Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly	
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Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala	
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Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp	
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Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln	
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Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro	
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Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val	
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Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu	
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Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp	
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Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile	
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Cys	Arg	Asn	Met	Trp	Ser	Gly	Thr	Phe	Pro	Ile	Asn	Ala	Tyr	Thr	Thr	
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Arg	Phe	Ala	Pro	Pro	Cys	Lys	Pro	Leu	Leu	Arg	Glu	Glu	Val	Ser	Phe	
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Pro	Glu	Pro	Asp	Val	Ala	Val	Leu	Thr	Ser	Met	Leu	Thr	Asp	Pro	Ser	
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His	Ile	Thr	Ala	Glu	Ala	Ala	Gly	Arg	Arg	Leu	Ala	Arg	Gly	Ser	Pro	
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Val	Glu	Ser	Glu	Asn	Lys	Val	Val	Ile	Leu	Asp	Ser	Phe	Asp	Pro	Leu	
	1005					1010					1015					
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Val	Ala	Glu	Glu	Asp	Glu	Arg	Glu	Ile	Ser	Val	Pro	Ala	Glu	Ile	Leu	

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Asp Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu				
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Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro				
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Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr				
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Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser				
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Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro				
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Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser				
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Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly				
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Ser Trp Ser Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys				
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Cys Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala				
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Ala Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu				
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Arg His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln				
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Arg Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His				
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Tyr Gln Asp Val Leu Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys				
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Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His	
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Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His	
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Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys	
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Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile	
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Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr	
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Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Cys	
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Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp	
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Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro	
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Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe  
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Ile	Asp	Ile	Leu	Ala	Gly	Tyr	Gly	Ala	Gly	Val	Ala	Gly	Ala	Leu	Val	610	615	620
Ala	Phe	Lys	Ile	Met	Ser	Gly	Glu	Val	Pro	Ser	Thr	Glu	Asp	Leu	Val	625	630	635
Asn	Leu	Leu	Pro	Ala	Ile	Leu	Ser	Pro	Gly	Ala	Leu	Val	Val	Gly	Val	645	650	655
Val	Cys	Ala	Ala	Ile	Leu	Arg	Arg	His	Val	Gly	Pro	Gly	Glu	Gly	Ala	660	665	670
Val	Gln	Trp	Met	Asn	Arg	Leu	Ile	Ala	Phe	Ala	Ser	Arg	Gly	Asn	His	675	680	685
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Ser	Gly	Thr	Phe	Pro	Ile	Asn	Ala	Tyr	Thr	Thr	Gly	Pro	Cys	Thr	Pro	820	825	830
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Phe	Phe	Thr	Glu	Leu	Asp	Gly	Val	Arg	Leu	His	Arg	Phe	Ala	Pro	Pro	885	890	895
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Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys	
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Asp Glu Cys His Ser Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr	
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gtc ctt gac caa gca gag act gcg ggg gcg aga ctg gtt gtg ctc gcc	12999
Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala	
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acc gcc acc cct ccg ggc tcc gtc act gtg ccc cat ccc aac atc gag	13047
Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu	
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Glu Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala	
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Ile Pro Leu Glu Val Ile Lys Gly Gly Arg His Leu Ile Phe Cys His	
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Leu	Gly	Lys	Val	Leu	Ile	Asp	Ile	Leu	Ala	Gly	Tyr	Gly	Ala	Gly	Val			
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Thr	Glu	Asp	Leu	Val	Asn	Leu	Leu	Pro	Ala	Ile	Leu	Ser	Pro	Gly	Ala			
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ccg	ggc	gag	ggg	gca	gtg	cag	tg	atg	aac	cgg	ctg	ata	gcc	ttc	gcc	14727		
Pro	Gly	Glu	Gly	Ala	Val	Gln	Trp	Met	Asn	Arg	Leu	Ile	Ala	Phe	Ala			
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Ser	Arg	Gly	Asn	His	Val	Ser	Pro	Thr	His	Tyr	Val	Pro	Glu	Ser	Asp			
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Leu	Leu	Arg	Arg	Leu	His	Gln	Trp	Ile	Ser	Ser	Glu	Cys	Thr	Thr	Pro			
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Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu	
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Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp	
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Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp	
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1870

1875

1880

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Gly Gly Ala Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp  
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Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser  
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35 40 45  
Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly  
50 55 60  
Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser  
65 70 75 80  
Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala  
85 90 95  
Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro  
100 105 110  
Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser  
115 120 125  
Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val  
130 135 140

Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys  
145 150 155 160

Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala  
165 170 175

Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val  
180 185 190

Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe  
195 200 205

Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe  
210 215 220

Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp  
225 230 235 240

Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro  
245 250 255

Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe  
260 265 270

Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr  
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Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn  
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Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly  
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Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr  
325 330 335

Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr  
340 345 350

Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp  
355 360 365

Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu  
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Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile Thr Leu Thr His Pro  
385 390 395 400

Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val  
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Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala  
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Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val Gly Arg Val Val Leu  
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Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu  
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Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln  
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Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu  
485 490 495

Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val Gln Thr  
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Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys His Met Trp Asn Phe  
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Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn  
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Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro  
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Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala  
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Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu  
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Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val  
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Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val  
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Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala  
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Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His  
675 680 685

Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val  
690 695 700

Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu  
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His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp  
725 730 735

Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys  
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Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe  
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Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile  
770 775 780

Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys  
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Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp  
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Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln Val Pro Ser Pro Glu  
865 870 875 880

Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His Arg Phe Ala Pro Pro  
885 890 895

Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe Arg Val Gly Leu His  
900 905 910

Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val  
915 920 925

Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu  
930 935 940

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945 950 955 960

Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  
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Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn Leu Leu  
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<213> Artificial Sequence

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<223> Description of Artificial Sequence:  
pd.delta.NS3NS5.pj.core140

<220>  
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<222> (12679)..(18411)

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ccaagcagga atcaatttct ttaatgaggc ttccagaatt gttgcttttt gcgtcttgta 480  
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ataggttagt tcagcagcac ataatgctat tttctcacct gaaggtcttt caaacctttc 660  
cacaaactga cgaacaagca ccttaggtgg tgttttacat aatatatcaa attgtggcat 720  
gcttagcgcc gatcttgtgt gcaattgata tctagtttca actactctat ttatcttgta 780  
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Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr	
575 580 585	
gcc ttt gtg ggc gct ggc tta gct ggc gcc gcc atc ggc agt gtt gga	14487
Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly	
590 595 600	
ctg ggg aag gtc ctc ata gac atc ctt gca ggg tat ggc gcg ggc gtg	14535
Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val	
605 610 615	
gcg gga gct ctt gtg gca ttc aag atc atg agc ggt gag gtc ccc tcc	14583
Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser	
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Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala	
640 645 650	
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Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly	
655 660 665	
ccg ggc gag ggg gca gtg cag tgg atg aac cgg ctg ata gcc ttc gcc	14727
Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala	
670 675 680	
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Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp	
685 690 695	
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Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln	
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ctc ctg agg cga ctg cac cag tgg ata agc tcg gag tgt acc act cca	14871
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720 725 730	
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Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val	
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cct ggg atc ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg gtc tgg	15015
Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp	
765 770 775	
cga ggg gac ggc atc atg cac act cgc tgc cac tgt gga gct gag atc	15063
Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile	
780 785 790 795	
act gga cat gtc aaa aac ggg acg atg agg atc gtc ggt cct agg acc	15111







Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp  
1485 1490 1495

tta gtc gtt atc tgt gaa agc gcg ggg gtc cag gag gac gcg gcg agc 17223  
Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser  
1500 1505 1510 1515

ctg aga gcc ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg 17271  
Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly  
1520 1525 1530

gac ccc cca caa cca gaa tac gac ttg gag ctc ata aca tca tgc tcc 17319  
Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser  
1535 1540 1545

tcc aac gtg tca gtc gcc cac gac ggc gct gga aag agg gtc tac tac 17367  
Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr  
1550 1555 1560

ctc acc cgt gac cct aca acc ccc ctc gcg aga gct gcg tgg gag aca 17415  
Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr  
1565 1570 1575

gca aga cac act cca gtc aat tcc tgg cta ggc aac ata atc atg ttt 17463  
Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe  
1580 1585 1590 1595

gcc ccc aca ctg tgg gcg agg atg ata ctg atg acc cat ttc ttt agc 17511  
Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser  
1600 1605 1610

gtc ctt ata gcc agg gac cag ctt gaa cag gcc ctc gat tgc gag atc 17559  
Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile  
1615 1620 1625

tac ggg gcc tgc tac tcc ata gaa cca ctg gat cta cct cca atc att 17607  
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1630 1635 1640

caa aga ctc cat ggc ctc agc gca ttt tca ctc cac agt tac tct cca 17655  
Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro  
1645 1650 1655

ggt gaa atc aat agg gtg gcc gca tgc ctc aga aaa ctt ggg gta ccg 17703  
Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro  
1660 1665 1670 1675

ccc ttg cga gct tgg aga cac cgg gcc cgg agc gtc cgc gct agg ctt 17751  
Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu  
1680 1685 1690

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Leu Ala Arg Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn  
1695 1700 1705

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Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly





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<211> 1911  
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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:

pd.delta.NS3NS5.pj.core140

<400> 17

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Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly  
35 40 45  
Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly  
50 55 60  
Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser  
65 70 75 80  
Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala  
85 90 95  
Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro  
100 105 110  
Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser  
115 120 125  
Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val  
130 135 140  
Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys  
145 150 155 160  
Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala  
165 170 175  
Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val  
180 185 190  
Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe  
195 200 205  
Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe  
210 215 220  
Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp  
225 230 235 240  
Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro  
245 250 255  
Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe  
260 265 270

Asp	Ser	Ser	Val	Leu	Cys	Glu	Cys	Tyr	Asp	Ala	Gly	Cys	Ala	Trp	Tyr		
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Glu	Leu	Thr	Pro	Ala	Glu	Thr	Thr	Val	Arg	Leu	Arg	Ala	Tyr	Met	Asn		
	290					295					300						
Thr	Pro	Gly	Leu	Pro	Val	Cys	Gln	Asp	His	Leu	Glu	Phe	Trp	Glu	Gly		
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Val	Phe	Thr	Gly	Leu	Thr	His	Ile	Asp	Ala	His	Phe	Leu	Ser	Gln	Thr		
				325					330					335			
Lys	Gln	Ser	Gly	Glu	Asn	Leu	Pro	Tyr	Leu	Val	Ala	Tyr	Gln	Ala	Thr		
			340					345					350				
Val	Cys	Ala	Arg	Ala	Gln	Ala	Pro	Pro	Pro	Ser	Trp	Asp	Gln	Met	Trp		
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Lys	Cys	Leu	Ile	Arg	Leu	Lys	Pro	Thr	Leu	His	Gly	Pro	Thr	Pro	Leu		
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Leu	Tyr	Arg	Leu	Gly	Ala	Val	Gln	Asn	Glu	Ile	Thr	Leu	Thr	His	Pro		
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Val	Thr	Lys	Tyr	Ile	Met	Thr	Cys	Met	Ser	Ala	Asp	Leu	Glu	Val	Val		
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Thr	Ser	Thr	Trp	Val	Leu	Val	Gly	Gly	Val	Leu	Ala	Ala	Leu	Ala	Ala		
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Tyr	Cys	Leu	Ser	Thr	Gly	Cys	Val	Val	Ile	Val	Gly	Arg	Val	Val	Leu		
	435						440					445					
Ser	Gly	Lys	Pro	Ala	Ile	Ile	Pro	Asp	Arg	Glu	Val	Leu	Tyr	Arg	Glu		
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Phe	Asp	Glu	Met	Glu	Glu	Cys	Ser	Gln	His	Leu	Pro	Tyr	Ile	Glu	Gln		
465					470					475					480		
Gly	Met	Met	Leu	Ala	Glu	Gln	Phe	Lys	Gln	Lys	Ala	Leu	Gly	Leu	Leu		
				485					490					495			
Gln	Thr	Ala	Ser	Arg	Gln	Ala	Glu	Val	Ile	Ala	Pro	Ala	Val	Gln	Thr		
			500					505					510				
Asn	Trp	Gln	Lys	Leu	Glu	Thr	Phe	Trp	Ala	Lys	His	Met	Trp	Asn	Phe		
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Ile	Ser	Gly	Ile	Gln	Tyr	Leu	Ala	Gly	Leu	Ser	Thr	Leu	Pro	Gly	Asn		
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Pro	Ala	Ile	Ala	Ser	Leu	Met	Ala	Phe	Thr	Ala	Ala	Val	Thr	Ser	Pro		
545					550					555					560		
Leu	Thr	Thr	Ser	Gln	Thr	Leu	Leu	Phe	Asn	Ile	Leu	Gly	Gly	Trp	Val		
				565					570					575			

Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala  
580 585 590

Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu  
595 600 605

Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val  
610 615 620

Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val  
625 630 635 640

Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val  
645 650 655

Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala  
660 665 670

Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His  
675 680 685

Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val  
690 695 700

Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu  
705 710 715 720

His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp  
725 730 735

Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys  
740 745 750

Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe  
755 760 765

Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile  
770 775 780

Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys  
785 790 795 800

Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp  
805 810 815

Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro  
820 825 830

Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp Arg Val Ser Ala Glu  
835 840 845

Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe His Tyr Val Thr Gly  
850 855 860

Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln Val Pro Ser Pro Glu  
865 870 875 880



Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys  
185 1190 1195 1200

Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu  
1205 1210 1215

Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys Lys Val  
1220 1225 1230

Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu  
1235 1240 1245

Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser  
1250 1255 1260

Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys  
265 1270 1275 1280

Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val  
1285 1290 1295

Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr  
1300 1305 1310

Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln  
1315 1320 1325

Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp  
1330 1335 1340

Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr  
345 1350 1355 1360

Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser  
1365 1370 1375

Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys  
1380 1385 1390

Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val  
1395 1400 1405

Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp  
1410 1415 1420

Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu  
425 1430 1435 1440

Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr  
1445 1450 1455

Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr  
1460 1465 1470

Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu  
1475 1480 1485





Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu  
 1795 1800 1805

Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser  
 1810 1815 1820

Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro Ile Pro Lys Ala Arg  
 825 1830 1835 1840

Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly Tyr Pro Trp Pro Leu  
 1845 1850 1855

Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp Leu Leu Ser Pro Arg  
 1860 1865 1870

Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro Arg Arg Arg Ser Arg  
 1875 1880 1885

Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu  
 1890 1895 1900

Met Gly Tyr Ile Pro Leu Val  
 905 1910

<210> 18

<211> 20247

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:  
 pd.delta.NS3NS5.pj.core150

<220>

<221> CDS

<222> (12679)..(18441)

<400> 18

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 gaattggtat aaagtttttg tttttgtaaa tctcgaagta tactcaaacg aatttagtat 240  
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	Met	Ala	Ala	Tyr	Ala	Ala	Gln	Gly	Tyr	Lys	Val	
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Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr												
	15				20				25			
atg tcc aag gct cat ggg atc gat cct aac atc agg acc ggg gtg aga												12807
Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg												
	30				35				40			
aca att acc act ggc agc ccc atc acg tac tcc acc tac ggc aag ttc												12855
Thr Ile Thr Thr Gly Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe												
	45				50				55			
ctt gcc gac ggc ggg tgc tcg ggg ggc gct tat gac ata ata att tgt												12903
Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys												
	60				65				70			75
gac gag tgc cac tcc acg gat gcc aca tcc atc ttg ggc att ggc act												12951
Asp Glu Cys His Ser Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr												
				80					85			90
gtc ctt gac caa gca gag act gcg ggg gcg aga ctg gtt gtg ctc gcc												12999
Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala												
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acc gcc acc cct ccg ggc tcc gtc act gtg ccc cat ccc aac atc gag												13047
Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu												
				110					115			120
gag gtt gct ctg tcc acc acc gga gag atc cct ttt tac ggc aag gct												13095
Glu Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala												
	125								130			135
atc ccc ctc gaa gta atc aag ggg ggg aga cat ctc atc ttc tgt cat												13143
Ile Pro Leu Glu Val Ile Lys Gly Gly Arg His Leu Ile Phe Cys His												
	140				145				150			155
tca aag aag aag tgc gac gaa ctc gcc gca aag ctg gtc gca ttg ggc												13191
Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly												
				160					165			170
atc aat gcc gtg gcc tac tac cgc ggt ctt gac gtg tcc gtc atc ccg												13239
Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro												
				175					180			185
acc agc ggc gat gtt gtc gtc gtg gca acc gat gcc ctc atg acc ggc												13287
Thr Ser Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly												
				190					195			200
tat acc ggc gac ttc gac tcg gtg ata gac tgc aat acg tgt gtc acc												13335
Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr												
	205								210			215
cag aca gtc gat ttc agc ctt gac cct acc ttc acc att gag aca atc												13383
Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile												

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	270 275 280			
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	285 290 295			
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	300 305 310 315			
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	320 325 330			
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	335 340 345			
gcg tac caa gcc acc gtg tgc gct agg gct caa gcc cct ccc cca tcg	Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser	13767		
	350 355 360			
tgg gac cag atg tgg aag tgt ttg att cgc ctc aag ccc acc ctc cat	Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His	13815		
	365 370 375			
ggg cca aca ccc ctg cta tac aga ctg ggc gct gtt cag aat gaa atc	Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile	13863		
	380 385 390 395			
acc ctg acg cac cca gtc acc aaa tac atc atg aca tgc atg tcg gcc	Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala	13911		
	400 405 410			
gac ctg gag gtc gtc acg agc acc tgg gtg ctc gtt ggc ggc gtc ctg	Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu	13959		
	415 420 425			
gct gct ttg gcc gcg tat tgc ctg tca aca ggc tgc gtg gtc ata gtg	Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val	14007		
	430 435 440			
ggc agg gtc gtc ttg tcc ggg aag ccg gca atc ata cct gac agg gaa	Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu	14055		
	445 450 455			

gtc ctc tac cga gag ttc gat gag atg gaa gag tgc tct cag cac tta	14103
Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu	
460 465 470 475	
ccg tac atc gag caa ggg atg atg ctc gcc gag cag ttc aag cag aag	14151
Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys	
480 485 490	
gcc ctc ggc ctc ctg cag acc gcg tcc cgt cag gca gag gtt atc gcc	14199
Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala	
495 500 505	
cct gct gtc cag acc aac tgg caa aaa ctc gag acc ttc tgg gcg aag	14247
Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys	
510 515 520	
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His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser	
525 530 535	
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Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala	
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Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile	
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Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr	
575 580 585	
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Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly	
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Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val	
605 610 615	
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Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser	
620 625 630 635	
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Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala	
640 645 650	
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Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly	
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Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala	
670 675 680	
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Ala	Ala	Ala	Arg	Val	Thr	Ala	Ile	Leu	Ser	Ser	Leu	Thr	Val	Thr	Gln	
700					705				710						715	
ctc	ctg	agg	cga	ctg	cac	cag	tgg	ata	agc	tcg	gag	tgt	acc	act	cca	14871
Leu	Leu	Arg	Arg	Leu	His	Gln	Trp	Ile	Ser	Ser	Glu	Cys	Thr	Thr	Pro	
				720				725							730	
tgc	tcc	ggc	tcc	tgg	cta	agg	gac	atc	tgg	gac	tgg	ata	tgc	gag	gtg	14919
Cys	Ser	Gly	Ser	Trp	Leu	Arg	Asp	Ile	Trp	Asp	Trp	Ile	Cys	Glu	Val	
			735					740						745		
ttg	agc	gac	ttt	aag	acc	tgg	cta	aaa	gct	aag	ctc	atg	cca	cag	ctg	14967
Leu	Ser	Asp	Phe	Lys	Thr	Trp	Leu	Lys	Ala	Lys	Leu	Met	Pro	Gln	Leu	
			750					755					760			
cct	ggg	atc	ccc	ttt	gtg	tcc	tgc	cag	cgc	ggg	tat	aag	ggg	gtc	tgg	15015
Pro	Gly	Ile	Pro	Phe	Val	Ser	Cys	Gln	Arg	Gly	Tyr	Lys	Gly	Val	Trp	
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cga	ggg	gac	ggc	atc	atg	cac	act	cgc	tgc	cac	tgt	gga	gct	gag	atc	15063
Arg	Gly	Asp	Gly	Ile	Met	His	Thr	Arg	Cys	His	Cys	Gly	Ala	Glu	Ile	
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act	gga	cat	gtc	aaa	aac	ggg	acg	atg	agg	atc	gtc	ggc	cct	agg	acc	15111
Thr	Gly	His	Val	Lys	Asn	Gly	Thr	Met	Arg	Ile	Val	Gly	Pro	Arg	Thr	
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tgc	agg	aac	atg	tgg	agt	ggg	acc	ttc	ccc	att	aat	gcc	tac	acc	acg	15159
Cys	Arg	Asn	Met	Trp	Ser	Gly	Thr	Phe	Pro	Ile	Asn	Ala	Tyr	Thr	Thr	
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Gly	Pro	Cys	Thr	Pro	Leu	Pro	Ala	Pro	Asn	Tyr	Thr	Phe	Ala	Leu	Trp	
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Arg	Val	Ser	Ala	Glu	Glu	Tyr	Val	Glu	Ile	Arg	Gln	Val	Gly	Asp	Phe	
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cac	tac	gtg	acg	ggc	atg	act	act	gac	aat	ctt	aaa	tgc	ccg	tgc	cag	15303
His	Tyr	Val	Thr	Gly	Met	Thr	Thr	Asp	Asn	Leu	Lys	Cys	Pro	Cys	Gln	
					865					870					875	
gtc	cca	tcg	ccc	gaa	ttt	ttc	aca	gaa	ttg	gac	ggg	gtg	cgc	cta	cat	15351
Val	Pro	Ser	Pro	Glu	Phe	Phe	Thr	Glu	Leu	Asp	Gly	Val	Arg	Leu	His	
				880					885						890	
agg	ttt	gcg	ccc	ccc	tgc	aag	ccc	ttg	ctg	cgg	gag	gag	gta	tca	ttc	15399
Arg	Phe	Ala	Pro	Pro	Cys	Lys	Pro	Leu	Leu	Arg	Glu	Glu	Val	Ser	Phe	
				895				900							905	
aga	gta	gga	ctc	cac	gaa	tac	ccg	gta	ggg	tcg	caa	tta	cct	tgc	gag	15447
Arg	Val	Gly	Leu	His	Glu	Tyr	Pro	Val	Gly	Ser	Gln	Leu	Pro	Cys	Glu	

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Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser			
925	930	935	
cat ata aca gca gag gcg gcc ggg cga agg ttg gcg agg gga tca ccc			15543
His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro			
940	945	950	955
ccc tct gtg gcc agc tcc tcg gct agc cag cta tcc gct cca tct ctc			15591
Pro Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu			
	960	965	970
aag gca act tgc acc gct aac cat gac tcc cct gat gct gag ctc ata			15639
Lys Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile			
	975	980	985
gag gcc aac ctc cta tgg agg cag gag atg ggc ggc aac atc acc agg			15687
Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg			
	990	995	1000
gtt gag tca gaa aac aaa gtg gtg att ctg gac tcc ttc gat ccg ctt			15735
Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu			
1005	1010	1015	
gtg gcg gag gag gac gag cgg gag atc tcc gta ccc gca gaa atc ctg			15783
Val Ala Glu Glu Asp Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu			
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cgg aag tct cgg aga ttc gcc cag gcc ctg ccc gtt tgg gcg cgg ccg			15831
Arg Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro			
	1040	1045	1050
gac tat aac ccc ccg cta gtg gag acg tgg aaa aag ccc gac tac gaa			15879
Asp Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu			
	1055	1060	1065
cca cct gtg gtc cat ggc tgc ccg ctt cca cct cca aag tcc cct cct			15927
Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro			
1070	1075	1080	
gtg cct ccg cct cgg aag aag cgg acg gtg gtc ctc act gaa tca acc			15975
Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr			
1085	1090	1095	
cta tct act gcc ttg gcc gag ctc gcc acc aga agc ttt ggc agc tcc			16023
Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser			
1100	1105	1110	1115
tca act tcc ggc att acg ggc gac aat acg aca aca tcc tct gag ccc			16071
Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro			
	1120	1125	1130
gcc cct tct ggc tgc ccc ccc gac tcc gac gct gag tcc tat tcc tcc			16119
Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser			
	1135	1140	1145



Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala	
1375 1380 1385	
tgg aag tcc aag aaa acc cca atg ggg ttc tcg tat gat acc cgc tgc	16887
Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys	
1390 1395 1400	
ttt gac tcc aca gtc act gag agc gac atc cgt acg gag gag gca atc	16935
Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile	
1405 1410 1415	
tac caa tgt tgt gac ctc gac ccc caa gcc cgc gtg gcc atc aag tcc	16983
Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser	
1420 1425 1430 1435	
ctc acc gag agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg	17031
Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly	
1440 1445 1450	
gag aac tgc ggc tat cgc agg tgc cgc gcg agc ggc gta ctg aca act	17079
Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr	
1455 1460 1465	
agc tgt ggt aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt	17127
Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys	
1470 1475 1480	
cga gcc gca ggg ctc cag gac tgc acc atg ctc gtg tgt ggc gac gac	17175
Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp	
1485 1490 1495	
tta gtc gtt atc tgt gaa agc gcg ggg gtc cag gag gac gcg gcg agc	17223
Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser	
1500 1505 1510 1515	
ctg aga gcc ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg	17271
Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly	
1520 1525 1530	
gac ccc cca caa cca gaa tac gac ttg gag ctc ata aca tca tgc tcc	17319
Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser	
1535 1540 1545	
tcc aac gtg tca gtc gcc cac gac ggc gct gga aag agg gtc tac tac	17367
Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr	
1550 1555 1560	
ctc acc cgt gac cct aca acc ccc ctc gcg aga gct gcg tgg gag aca	17415
Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr	
1565 1570 1575	
gca aga cac act cca gtc aat tcc tgg cta ggc aac ata atc atg ttt	17463
Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe	
1580 1585 1590 1595	
gcc ccc aca ctg tgg gcg agg atg ata ctg atg acc cat ttc ttt agc	17511
Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser	





atc ccc aag gct cgt cgg ccc gag ggc agg acc tgg gct cag ccc ggg 18231  
 Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly  
 1840 1845 1850  
  
 tac cct tgg ccc ctc tat ggc aat gag ggc tgc ggg tgg gcg gga tgg 18279  
 Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp  
 1855 1860 1865  
  
 ctc ctg tct ccc cgt ggc tct cgg cct agc tgg ggc ccc aca gac ccc 18327  
 Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro  
 1870 1875 1880  
  
 cgg cgt agg tcg cgc aat ttg ggt aag gtc atc gat acc ctt acg tgc 18375  
 Arg Arg Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys  
 1885 1890 1895  
  
 ggc ttc gcc gac ctc atg ggg tac ata ccg ctc gtc ggc gcc cct ctt 18423  
 Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu  
 1900 1905 1910 1915  
  
 gga ggc gct gcc agg gcc taatagtcga ctttgttccc actgtacttt 18471  
 Gly Gly Ala Ala Arg Ala  
 1920  
  
 tagctcgtac aaaataacaat atactttttca tttctccgta aacaacatgt tttcccatgt 18531  
 aatatccttt tctatttttc gttccgttac caactttaca catactttat atagctattc 18591  
 acttctatac actaaaaaac taagacaatt ttaattttgc tgccctgccat atttcaattt 18651  
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 cgctgcttc aaaccgctaa caatacctgg gccaccaca ccgtgtgcat tcgtaatgtc 19671  
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 gtcagcaaat tttctgtctt cgaagagtaa aaaattgtac ttggcggata atgcctttag 19791  
 cggcttaact gtgccctcca tggaaaaatc agtcaagata tccacatgtg tttttagtaa 19851  
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 caatgaagca cacaagtttg tttgcttttc gtgcatgata ttaaataagct tggcagcaac 19971  
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 <213> Artificial Sequence

<220>  
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 20 25 30  
 Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly  
 35 40 45  
 Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly  
 50 55 60  
 Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser  
 65 70 75 80  
 Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala  
 85 90 95  
 Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro  
 100 105 110



Thr	Ser	Thr	Trp	Val	Leu	Val	Gly	Gly	Val	Leu	Ala	Ala	Leu	Ala	Ala		
				420				425					430				
Tyr	Cys	Leu	Ser	Thr	Gly	Cys	Val	Val	Ile	Val	Gly	Arg	Val	Val	Leu		
		435					440					445					
Ser	Gly	Lys	Pro	Ala	Ile	Ile	Pro	Asp	Arg	Glu	Val	Leu	Tyr	Arg	Glu		
		450					455					460					
Phe	Asp	Glu	Met	Glu	Glu	Cys	Ser	Gln	His	Leu	Pro	Tyr	Ile	Glu	Gln		
465					470					475					480		
Gly	Met	Met	Leu	Ala	Glu	Gln	Phe	Lys	Gln	Lys	Ala	Leu	Gly	Leu	Leu		
				485					490					495			
Gln	Thr	Ala	Ser	Arg	Gln	Ala	Glu	Val	Ile	Ala	Pro	Ala	Val	Gln	Thr		
			500					505						510			
Asn	Trp	Gln	Lys	Leu	Glu	Thr	Phe	Trp	Ala	Lys	His	Met	Trp	Asn	Phe		
		515					520					525					
Ile	Ser	Gly	Ile	Gln	Tyr	Leu	Ala	Gly	Leu	Ser	Thr	Leu	Pro	Gly	Asn		
		530				535					540						
Pro	Ala	Ile	Ala	Ser	Leu	Met	Ala	Phe	Thr	Ala	Ala	Val	Thr	Ser	Pro		
545					550					555					560		
Leu	Thr	Thr	Ser	Gln	Thr	Leu	Leu	Phe	Asn	Ile	Leu	Gly	Gly	Trp	Val		
				565					570					575			
Ala	Ala	Gln	Leu	Ala	Ala	Pro	Gly	Ala	Ala	Thr	Ala	Phe	Val	Gly	Ala		
			580					585					590				
Gly	Leu	Ala	Gly	Ala	Ala	Ile	Gly	Ser	Val	Gly	Leu	Gly	Lys	Val	Leu		
		595					600					605					
Ile	Asp	Ile	Leu	Ala	Gly	Tyr	Gly	Ala	Gly	Val	Ala	Gly	Ala	Leu	Val		
	610					615					620						
Ala	Phe	Lys	Ile	Met	Ser	Gly	Glu	Val	Pro	Ser	Thr	Glu	Asp	Leu	Val		
625				630						635				640			
Asn	Leu	Leu	Pro	Ala	Ile	Leu	Ser	Pro	Gly	Ala	Leu	Val	Val	Gly	Val		
			645						650					655			
Val	Cys	Ala	Ala	Ile	Leu	Arg	Arg	His	Val	Gly	Pro	Gly	Glu	Gly	Ala		
			660					665					670				
Val	Gln	Trp	Met	Asn	Arg	Leu	Ile	Ala	Phe	Ala	Ser	Arg	Gly	Asn	His		
			675				680					685					
Val	Ser	Pro	Thr	His	Tyr	Val	Pro	Glu	Ser	Asp	Ala	Ala	Ala	Arg	Val		
	690					695					700						
Thr	Ala	Ile	Leu	Ser	Ser	Leu	Thr	Val	Thr	Gln	Leu	Leu	Arg	Arg	Leu		
705					710					715					720		

His	Gln	Trp	Ile	Ser	Ser	Glu	Cys	Thr	Thr	Pro	Cys	Ser	Gly	Ser	Trp	725	730	735
Leu	Arg	Asp	Ile	Trp	Asp	Trp	Ile	Cys	Glu	Val	Leu	Ser	Asp	Phe	Lys	740	745	750
Thr	Trp	Leu	Lys	Ala	Lys	Leu	Met	Pro	Gln	Leu	Pro	Gly	Ile	Pro	Phe	755	760	765
Val	Ser	Cys	Gln	Arg	Gly	Tyr	Lys	Gly	Val	Trp	Arg	Gly	Asp	Gly	Ile	770	775	780
Met	His	Thr	Arg	Cys	His	Cys	Gly	Ala	Glu	Ile	Thr	Gly	His	Val	Lys	785	790	795
Asn	Gly	Thr	Met	Arg	Ile	Val	Gly	Pro	Arg	Thr	Cys	Arg	Asn	Met	Trp	805	810	815
Ser	Gly	Thr	Phe	Pro	Ile	Asn	Ala	Tyr	Thr	Thr	Gly	Pro	Cys	Thr	Pro	820	825	830
Leu	Pro	Ala	Pro	Asn	Tyr	Thr	Phe	Ala	Leu	Trp	Arg	Val	Ser	Ala	Glu	835	840	845
Glu	Tyr	Val	Glu	Ile	Arg	Gln	Val	Gly	Asp	Phe	His	Tyr	Val	Thr	Gly	850	855	860
Met	Thr	Thr	Asp	Asn	Leu	Lys	Cys	Pro	Cys	Gln	Val	Pro	Ser	Pro	Glu	865	870	875
Phe	Phe	Thr	Glu	Leu	Asp	Gly	Val	Arg	Leu	His	Arg	Phe	Ala	Pro	Pro	885	890	895
Cys	Lys	Pro	Leu	Leu	Arg	Glu	Glu	Val	Ser	Phe	Arg	Val	Gly	Leu	His	900	905	910
Glu	Tyr	Pro	Val	Gly	Ser	Gln	Leu	Pro	Cys	Glu	Pro	Glu	Pro	Asp	Val	915	920	925
Ala	Val	Leu	Thr	Ser	Met	Leu	Thr	Asp	Pro	Ser	His	Ile	Thr	Ala	Glu	930	935	940
Ala	Ala	Gly	Arg	Arg	Leu	Ala	Arg	Gly	Ser	Pro	Pro	Ser	Val	Ala	Ser	945	950	955
Ser	Ser	Ala	Ser	Gln	Leu	Ser	Ala	Pro	Ser	Leu	Lys	Ala	Thr	Cys	Thr	965	970	975
Ala	Asn	His	Asp	Ser	Pro	Asp	Ala	Glu	Leu	Ile	Glu	Ala	Asn	Leu	Leu	980	985	990
Trp	Arg	Gln	Glu	Met	Gly	Gly	Asn	Ile	Thr	Arg	Val	Glu	Ser	Glu	Asn	995	1000	1005
Lys	Val	Val	Ile	Leu	Asp	Ser	Phe	Asp	Pro	Leu	Val	Ala	Glu	Glu	Asp	1010	1015	1020



Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp  
1330 1335 1340

Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr  
345 1350 1355 1360

Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser  
1365 1370 1375

Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys  
1380 1385 1390

Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val  
1395 1400 1405

Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp  
1410 1415 1420

Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu  
425 1430 1435 1440

Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr  
1445 1450 1455

Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr  
1460 1465 1470

Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu  
1475 1480 1485

Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys  
1490 1495 1500

Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala Phe Thr  
505 1510 1515 1520

Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Gln Pro  
1525 1530 1535

Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val  
1540 1545 1550

Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro  
1555 1560 1565

Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro  
1570 1575 1580

Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe Ala Pro Thr Leu Trp  
585 1590 1595 1600

Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Val Leu Ile Ala Arg  
1605 1610 1615

Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile Tyr Gly Ala Cys Tyr  
1620 1625 1630

Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly  
 1635 1640 1645  
 Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg  
 1650 1655 1660  
 Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp  
 665 1670 1675 1680  
 Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg Gly Gly  
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 Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr  
 1700 1705 1710  
 Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp Leu Ser  
 1715 1720 1725  
 Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val  
 1730 1735 1740  
 Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu Leu Ala  
 745 1750 1755 1760  
 Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg Met Ser Thr Asn Pro  
 1765 1770 1775  
 Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg Pro Gln Asp  
 1780 1785 1790  
 Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu  
 1795 1800 1805  
 Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser  
 1810 1815 1820  
 Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro Ile Pro Lys Ala Arg  
 825 1830 1835 1840  
 Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly Tyr Pro Trp Pro Leu  
 1845 1850 1855  
 Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp Leu Leu Ser Pro Arg  
 1860 1865 1870  
 Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro Arg Arg Arg Ser Arg  
 1875 1880 1885  
 Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu  
 1890 1895 1900  
 Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu Gly Gly Ala Ala Arg  
 905 1910 1915 1920  
 Ala